"ROLE OF NON HDL CHOLESTEROL IN ASSESSING THE RISK OF DEVELOPMENT OF ISCHEMIC STROKE IN PATIENTS WITH ESTABLISHED CORONARY ARTERY DISEASE ON ATORVASTATIN THERAPY"

Dissertation submitted for
M.D. Degree Examination
Branch I – INTERNAL MEDICINE

DEPARTMENT OF INTERNAL MEDICINE
K.A.P.V Government Medical College,
Trichy

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY CHENNAI

APRIL-2013

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled "**Role of non HDL cholesterol in assessing the risk of development of ischemic stroke in patients with established coronary artery disease on atorvastatin therapy**"is the bonafide work done by **Dr.K.ArunaRamani**, under my direct guidance and supervision in the Department of Internal Medicine, K.A.P.V Government Medical College, Trichy-1, in fulfilment of regulations of the Tamil Nadu Dr. M.G.R. Medical University for the award of M.D.Degree branch I, Part II (General Medicine) during this period of study from May 2010 -April 2013.

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DECLARATION

I would like to sincerely declare that this dissertation titled “Role of non HDL cholesterol in assessing the risk of development of ischemic stroke in patients with established coronary artery disease on atorvastatin therapy” is done by me at K.A.P.V Govt. Medical College, Trichyduring 2010-2012 under the guidance and supervision of Prof. V.Rajendran, M.D.The dissertation is submitted to The Tamil Nadu Dr. M.G.R.Medical University towards the partial fulfilment of requirements for theaward of M.D. Degree (Branch I) in General Medicine.

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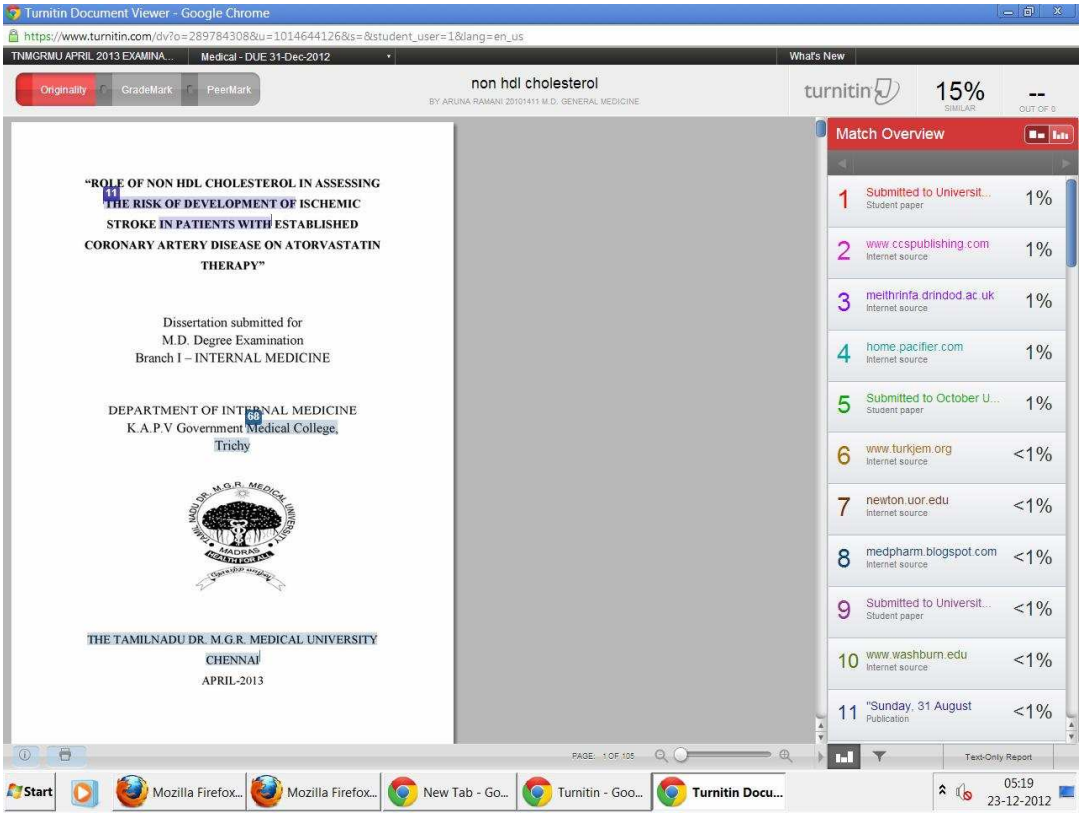
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INTRODUCTION

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For decades the role of LDL cholesterol in predicting the risk of coronary and cerebrovascular events has been well established. It is now clear that LDL is not the only atherogenic particle. But other particles that contain apoprotein B such as VLDL, VLDL remnants, IDL, and Chylomicron remnants are important. This is reflected in the non HDL cholesterol value which is a simple measure. It does not require fasting specimen.It is calculated by subtracting total cholesterol from HDL cholesterol. Patients on statin therapy have relatively low LDL cholesterol but still a significant number of patients develop a second coronary or cerebrovascular event. In those patients other parameters in lipid profile such as triglycerides, low HDL cholesterol, & lipoprotein a and other remnant lipoproteins are important. The terminology non HDL cholesterol which includes all cholesterols other than HDL has a significant role in assessing the second risk for subsequent development of coronary or cerebrovascular events in statin treated individuals. The study was conducted to stress the importance of other parameters of lipid profile in bringing down the ischemic events.

AIM

AIM

The aim is to study if non HDL cholesterol has got significant role in assessing the risk of ischemic stroke on established coronary artery disease patients who were on atorvastatin therapy.

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REVIEW OF LITERATURE

REVIEW OF LITERATURE

INTRODUCTION

Atherosclerosis and its sequel are the leading causes of mortality in this world. With increasing prevalence of sedentary life habits and fast food culture early onset obesity are increasing in prevalence. Because of widespread awareness there is increasing use of statin therapy. But still the risk of coronary and cerebrovascular events has not come down. This study was conducted for analysing lipids beyond LDL.

Garg *et al.,*[12] conducted a study to recognise the lipid parameter which has high levels of relation with both coronary artery disease and metabolic syndrome. They also had an aim of analysing the association of non HDL cholesterol and metabolic syndrome in particular among people residing in north India.

Their study included: One hundred and thirteen Coronary artery disease patients & involved one hundred and forty non-coronary artery disease patients as controls between the ages thirty five and seventy five years. Both cases and controls were matched for race and geography.

Consent was obtained from both the controls and cases in writing. The study identified cases on the basis of history and standard

investigations. They measured Height, weight, waist and hip circumferences, blood pressures (systolic and diastolic) and lipid profile.

The study concluded that Sixty nine among 113 (61.06%) of coronary artery disease patients and fifty two among one hundred and thirty (37.1%) of non-coronary artery disease patients had metabolic syndrome.

The CAD patients were identified based on their medical diagnostic history. Height, weight, waist and hip circumferences, blood pressures (systolic and diastolic) and lipid profile were measured for all the subjects. Age standardized presence of abnormalities in coronary artery disease was in the following order. Abdominal obesity had the best correlation followed by non-High density lipoprotein cholesterol which was followed by systolic blood pressure.

The triglycerides, total cholesterol values and low density lipoproteins and HDL cholesterol had lesser significance and had decreasing value of correlation in that order. This specifies the role played by non-high density lipoprotein cholesterol by acting as a screening measure to identify patients with metabolic syndrome to assess their coronary vascular risk.

Sigedel *et al.*,[28] conducted a study to assess if non HDL cholesterol was an important measure in assessing CAD risk. Total cholesterol values

and low density lipoprotein cholesterol values are being used as correlative markers for many years. But many studies have reported non-High density cholesterol as an important and easy measure, since non High density lipoprotein can be calculated by deducting High density cholesterol from total amount of cholesterol.

It was a cross sectional study. Fifty one myocardial infarction patients and same number of controls clinical history electro and echo cardiography and enzyme analysis were used to diagnose myocardial infarction .Non HDL cholesterol values were obtained by deducting high density lipoprotein from total cholesterol.

The results were statistically analysed. Forty two myocardial infarction cases had abnormal lipid profile in contrast to twenty of the controls. The study concluded that High density lipoprotein cholesterol had a better correlation followed by non-High density lipoprotein cholesterol. In this study non HDL cholesterol had a p value of o.o2 and low density lipoprotein had a p value of 0.05. The study concluded that HDL Cholesterol and non-high density cholesterol serve as a better measure than low density lipoprotein.

Vaccaro *et al.*,[33.]A study was conducted by Vaccaro et al to find the relationship between lifestyle changes advised by medical faculty &non high density lipoprotein cholesterol values. The study was done in

United States among various. It collected data from national surveys. It concluded that minority population of UNITED STATES had received more dietary advice. Eighty per cent followed the advice. Those who were then practising weight reducing measures had low non high density cholesterol values. It stressed upon greater motivation to follow these goals persistently.

Kelley *et al.*,[33]. Their study used meta-analysis methods to evaluate non high density lipoprotein cholesterol values and diet and outdoor exercise. It included all randomised control trial in adults. On analysing various data the study concluded that there was no significant differences between the various studies and exercise and diet modifications caused reduction of non-high density lipoprotein cholesterol among various subjects.

Sniderman *et al.*,[34]. This study was conducted to analyse whether non high density lipoprotein cholesterol & apolipoprotein B were equal markers of atherosclerotic heart disease. This study got its data from the INTERHEART data base.

The INTERHEART study is a case control study of acute coronary syndrome with samples taken from nine thousand three hundred and forty five cases and twelve thousand one hundred and twenty cases with data from fifty two countries. In this study the apoprotein B and High density

lipoproteins were expressed in percentiles. Concordance was given by definition if apoprotein B contained normal cholesterol. It concluded that apoprotein B had better correlation value than non-High density lipoprotein though the difference was very minimal.

Rana *et al.*,[27] Though lipid lowering goals are widely practised with various medications still there is significant risk of coronary artery disease. So they conducted a study was done to look in depth about other parameters in the lipid profile. They conducted a study to assess the role played by non-high density lipoprotein cholesterol. “The third adult treatment panel ATP 3” formulated some guidelines for the “US National Cholesterol Education Program”. This panel introduced non HDL cholesterol as a secondary goal for therapy among people when triglyceride was more than two hundred. Meta-analysis also confirmed the role of non-high density lipoprotein as an important goal.

Jones *et al*,[2]In“the EPIC-Norfolk prospective population study”, twenty one thousand four hundred and forty eight people not suffering from diabetes or coronary artery disease were followed up for eleven years. People who had high non HDL cholesterol had increased risk of coronary events in spite of low LDLl values. Next I would like to review the topic from books

DISEASE SPECTRUM

Atherosclerosis affects varying circulatory compartments of the body but the manifestations are different. It affects the cerebral circulation and presents as transient ischemic events and stroke. It affects the coronary circulation and manifests as stable angina, unstable angina and myocardial infarction. It affects the renal arteries causing renal artery stenosis and it affects the peripheral vascular system causing claudication pain and even life threatening gangrene. All the atherosclerotic events are accelerated in a patient with diabetes mellitus.

INITIATING EVENT IN ATHEROSCLEROSIS[25]

Lipoproteins have high affinity for matrix extracellular proteins. When there is excess cholesterol they get deposited in the walls of arteries as fatty streak. They are the first macroscopic evidence of atherosclerosis. They generally adhere to tunica intima, the innermost layer of the arteries. They interact with glycosaminoglycan which causes difficulty in removal of these fatty streaks. They undergo various metabolic changes including oxidation which causes change in morphology and secures their place in the blood vessel.[3]

Leukocyte Recruitment

Once the fatty streaks are formed, there is ongoing inflammatory process and the release of various inflammatory mediators and the

recruitment of scavenger macrophages[18] and monocytes into the lesion thus begetting further inflammation.[4]

FOAM CELL FORMATION[27]

The monocytes thus recruited engulf lipoproteins by receptor mediated endocytosis and accumulate lipid and become the giant lipid laden macrophages otherwise called foam cells.

Evolution of atherosclerotic plaque and its effects

There are various complicating factors behind the development of a complex atheroma[19]. Many fatty streaks remain unmodified without causing any complication throughout life.

Hypercholesterolemia causes LDL-C to accumulate in intima. Matrix interactions cause oxidative reactions of lipoproteins and inflammatory reactions are initiated. Altered lipoprotein particles actively promote inflammation. Chemo attraction by various chemokines including macrophage attractant protein cause increased entry of lipoproteins into the zone.

As the lesion matures smooth muscle cells migrate superficially from the layer of media into the layer of intima where they play an active role in attracting further inflammatory particles and increasing the size of the lesion

ROLE OF HDL

Now the question how to remove cholesterol from fatty streak arises**?** This is done by the reverse cholesterol transport. The key molecule here is our HDL cholesterol. This HDL with the help of ATP binding cassette transporters receives cholesterol from the nascent cell and thus reduces the size of the atheroma and its effects. The gene responsible here is the ABCA gene. The mutations of this genes cause the Tangiers disease in which we have the orange color enlarged tonsils causing premature atherosclerosis. This is one of the diseases characterized by remarkably low HDL levels.

The HDL thus loaded with cholesterol reaches the liver. In the liver it binds to the receptors responsible for scavenging which are the B 1 receptors. Liver metabolizes the cholesterols into bile acids and are excreted through the bile. This pathway is called the reverse cholesterol transport and this is responsible for the anti atherogenic effect of HDL cholesterol and it thus receives its name the good cholesterol[37]

Plaque natural course and termination in rupture[20]

Plaques with very paper thin fibrous caps and huge lipid core material and a marked content of macrophages are more prone for rupture. On the other hand plaques with thick fibrous cap more smooth

muscles on the surface less amount of fats and macrophages are less likely to rupture and cause fatal events

Factors involved in assessing risk of rupture of plaque[24]

LDL particle dimension ,levels of homocysteine , high sensitive C reactive protein, phospholipase A2 measurements, fibrinogen content, myeloperoxidase levels are all important factors in assessing the risk of coronary events. With increasing number of markers being identified every day we tend to lose focus on the primary marker. Still the main events in assessing risk are family history, previous history, serum lipid profile & glycemic status. These age old factors alone predict 95 % risk in all populations.

"The list below includes the risk factors identified through the current "National Cholesterol Education Project[32,33] Adult Treatment Panel III (ATP III).[8,9]

“**Major Risk Factors modifying low density lipoprotein targets.**[12]

Smoking

Hypertension JNC stage 1 and above

Reduced HDL cholesterol level of less than forty mg/dl

Diabetes

Family history of presence of coronary event

Coronary event in men who have first degree relative less than 55 years

Coronary event in in females with 1st degree relative less than 65 years

Age (men more than forty five years &women more than fifty five years)

Obesity

Sedentary habits

Diet high in saturated fats

Lipoprotein(a)

Homocysteine

Factors promoting thrombosis

Factors promoting inflammation

Abnormal blood sugar

HDL cholesterol of more than 60 mg/dl is thought to be as a negative risk factor. When it is present we can remove one risk factor.

When an individual has less than two risk factors the goal of LDL is <160 mg/dl. When there are two or more factors we have to calculate the risk of developing a coronary event in next ten years.

When the assessed risk is 20 % the target of Low density lipoprotein cholesterol is 130mg/dl.

When the individual is suffering from diabetes or when there is evidence of atherosclerosis or when the assessed risk is more than 20 % then the target LDL cholesterol level is significantly low that is <100 mg/dl. When the risk is markedly increased the goal is <70 mg/dl.

LDL Level, mmol/L (mg/dl)			
Categorisation of risk	**Goal**	**TLC initiation**	**Pharmacological treatment**
Markedly increased Acute coronary event with diabetes	<70	(70)	(70)
Increased risk	<100 optional target<70	(100)	100<=100
Moderately increased 2or more risk factors	<100	130	130
Moderate 2or more risk factors	<130	130	160
Low 0 or 1 risk factor	<160	160	190

The most important factors in achieving LDL goals are diet and exercise[38]

According to ATP 3 guidelines when the level of LDL cholesterol in our patient is more than thirty mg/dl than his desired target we should

intervene him with drugs. When the patient's triglycerides are elevated we should focus on the non HDL Cholesterol levels. This is simply done by deducting HDL cholesterol from total cholesterol values. The targets are slightly altered from the set points for LDL cholesterol by adding 3omg/dl more.

When LDL cholesterol levels have been lowered they don't actually cause a decrease in size of atheroma but instead they give more stabilization to the atheroma and prevent them from breaking down easily.

Statins the group of drugs that lower LDL cholesterol by inhibiting HMG CO A enzyme at night not only lower LDL levels but also has numerous additive effects on plaque morphology and physiology.

Ezetimibe is a novel class of agent that decreases absorption of cholesterol from duodenum and jejunum. It acts on a cholesterol transporter on the enterocyte named as Niemann pick like protein NPC1L1. It acts as adjunct drug in lowering LDL levels and in achieving the target. The efficacy and safety of the drug has not been established.

Beyond LDL

Though LDL cholesterol is the most important factor in monitoring cardio vascular risk status and subsequent follow up of risk reduction, the case is not always so.

In spite of risk reduction with reduction of LDL cholesterol levels in certain sub group of patients the risk of atherosclerotic events remains high. Other factors like Apo lipoproteins, lipoprotein a and c reactive proteins[14]have a say.

Non HDL cholesterol has a significant contribution in risk assessment and therapeutic goal monitoring especially when the triglycerides are high and in diabetes and in patients with metabolic syndrome.

So we have to consider other details of the lipid profile to bring down the disease incidence. Though we have reduced the LDL cholesterol levels well with statin therapy we still see a lot of coronary events. Decreased HDL levels are considered in these cases. HDL levels are inversely related to triglycerides. When the HDL levels are low the triglycerides level are high. So we are dealing with a dual problem. By losing weight and increasing physical activity we can greatly increase the HDL cholesterol and subsequently decrease the risk of coronary event.

Nicotinic acid or niacin is one drug which can significantly raise the high density lipoprotein levels. This has been proved by various trials and meta-analysis.

Flushing and pruritus are the major side effects associated with the consumption of niacin. This can be theoretically eliminated by the co administration of prostaglandin D receptor antagonist. This is under investigation and has not come to the markets. If this drug becomes successful it can eliminate the patient related factors in accepting niacin as a drug.

Nuclear receptors agonists are being developed to raise HDL levels. When patients were given peroxisome proliferator & activator of receptor alpha and gamma PPAR agonists they did not have very good reduction of cardiovascular events.

Paradoxically there was a significant increase in mortality. Hence these drugs are not recommended. Cholesteryl ester transfer protein CETP inhibitors also elevate high density lipoprotein levels. These agents are now under trial.

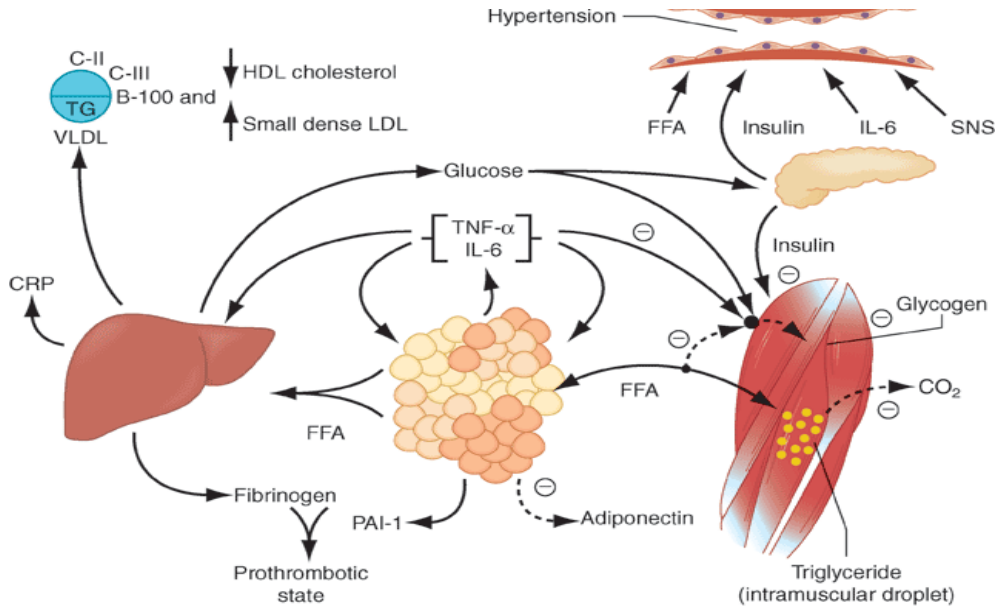
Diabetes Mellitus and its association with Insulin Resistance& Metabolic Syndrome

The leading cause of mortality in diabetes is complications due to atherosclerosis. With changing lifestyle and adaptation of unhealthy food practices these are considered as an epidemic now.

Diabetic dyslipidemia, the term used to describe abnormal lipid profile in type 2 diabetes mellitus is the key factor behind the

atherosclerosis which occurs prematurely in diabetes. Though the LDL levels in diabetes are not significantly altered but the size of the particles and their density is condensed in diabetes which increases atherosclerosis risk Also these patients have reduced LDL and increased triglyceride levels. Hypertension is also commonly prevalent in diabetes and obese individuals with dyslipidemia. These factors have been well recognized by the ATP 3 guidelines.

Pathophysiology of the metabolic syndrome



Free fatty acids are being liberated in large quantity out from an enlarged adipose tissue structure when they reach the liver they cause increased production of glucose by gluconeogenesis and triglycerides and results in the synthesis of VLDL. It also causes lipoprotein abnormalities like decrease in low density lipoprotein and increase in high density

lipoprotein. Free fatty acids cause reduction in sensitivity of muscle to insulin and their glucose uptake. When the glucose levels are high they stimulate the pancreas and cause release of insulin resulting in hyperinsulinemia. Hyperinsulinemia causes increase of sodium transport promoting sympathetic nervous system activity and also causes release of fatty acids as substrates for gluconeogenesis. Since the environment is ultimately proinflammatory they cause increase in insulin resistance. Interleukin 6 and tumor necrosis factor secreted by macrophages also cause increase in insulin resistance and elevation of triglycerides and release of free fatty acids. They also increase gluconeogenesis, very low density lipoprotein production and increase in insulin resistance by skeletal muscle, fibrinogen produced by liver and plasminogen activator inhibitor 1 produced by adipocytes cause the state to turn prothrombotic. Increased production of C-reactive protein by the liver also adds to the cause. Decreased synthesis of anti-inflammatory factors & the cytokine adiponectin which sensitizes insulin are associated with high prevalence of metabolic syndrome.

Overweight is a significant component of the metabolic syndrome. But what has a greater significance value is the abdominal obesity. So abdominal obesity is the single most measurement in assessing the metabolic syndrome. So we can identify majority of patients with

metabolic syndrome by measuring their abdominal girth. A simple inch tape is all that is required.

diagnosis of Metabolic Syndrome Any 3 Factors	
Risk Factor	**Cut off point**
Central obesity	
Male {waist circumference}	>=102 cm
Female	>=88 cm
Triglycerides	>=150 mg/dl
High density lipoprotein	
Male	<40 mg/dl
Female	<50 mg/dl
Blood pressure	130/85 mmHg
blood glucose while fasting	>110 mg/dl

Some patients especially men though they have only slight increase in waist circumference have other points in favour of the detection of metabolic syndrome. They have strong genetic influence for the development of metabolic syndrome. They should be advised diet and lifestyle changes

The main goal in the therapy of metabolic syndrome is proper education and counselling regarding the hazards of faulty diet habits and

physical inactivity. Half an hour of physical activity a day increases their life span by 6 to 7 years. The ATP 3 guidelines also stresses upon these factors.

Establishing proper glycaemic status reduces micro vesicular complications more than macro vesicular complications of diabetes. Hence early detection of diabetes and following patients periodically is important. It may even result in adverse events. So the ultimate goal is in correction of diabetic dyslipidaemia and other factors..

Multiple drug trials are being conducted keeping in mind the specific dyslipidaemia problems of diabetes. Statin therapy has been shown to have very high benefit beyond doubts. Other factors beyond tight glycaemic control are being looked upon.

Since the benefit of HMG CO A reductase inhibitors for diabetic populations are proved by meta-analysis. The American diabetic association recommends statins to all patients with total cholesterol above one hundred and thirty five.

Metformin is the only oral hypoglycaemic agent which is found to be cardio protective. Statins are not useful in chronic kidney disease especially in end stage.

Issues in assessing risk

A large number of markers of coronary event risk have been identified in recent years. Markers estimated by using peripheral arterial blood include size of low density lipoprotein particles & levels of blood homocysteine, Lipoprotein a, fibrinogen, C reactive protein, plasminogen activator inhibitor protein 1, tissue myeloperoxidase& lipoprotein related phospholipase A_2.

But still there is no substitute for careful history taking and analysis of serum lipid profile and fasting blood glucose.

With the existing clinical data we are not in a position to recommend imaging studies as a screening test in detecting underlying disease. Such methods include the usage carotid Doppler to study carotid intima media thickness, calcification, MR angiography and CT angiography. If these tests are used universally the patients may panic and this may increase the economic burden of the society

Use of these investigations requires further supportive evidence in order to be practiced**.**

ISCHEMIC HEART DISEASE

Pathophysiology

The basic pathophysiology in understanding a myocardial ischemia is demand supply mismatch. That is the demand between oxygen supply and coronary blood flow.

Whenever there is any demand for oxygen it is the work of myocardium to ensure that there is availability of adequate oxygen rich blood to the tissues in demand. When this does not happen that part of myocardium will suffer from ischemia.

The coronary circulation is regulated by the hearts oxygen needs on a minute by minute basis. This is achieved by the ability of coronary bed to greatly alter its resistance so that the myocardium always has a very high & almost stable fraction of oxygen. Ordinarily, intra myocardial resistance vessels have a greater capacity for dilation.

During exercise and emotion the heart needs to pump at a faster rate resulting in great changes in its oxygen need. This is accomplished by the change in vascular resistance to a great extent. This is termed metabolic regulation of coronary vascular bed.

The change in resistance of coronary vascular bed to changes in blood pressure that happens several times in a day is called auto regulation. Since the lumen of arteries is narrowed in atherosclerosis

when there is an increase in demand the required oxygen supply cannot be met. This results in ischemia. When there is severe obstruction even the blood supply at rest is reduced.

This results in rest angina. When spasms of vessels occur as in prinzmetals angina the blood supply is reduced also resulting in ischemia. Aortitis results in narrowing of the ostia and reduction in blood supply. Congenital anomalies like anomalous origin of left anterior descending artery from pulmonary artery can lead to myocardial ischemia in infancy which is a rare cause.

Coronary Atherosclerosis

Epicardial coronary arteries are the most common site for the development of atherosclerosis. Plaque formation and later rupture at segments is the cause of epicardial coronary vessel narrowing. When the rupture of plaque occurs platelets are recruited and activated and then the coagulation cascade is initiated and activated.

All this leads to accumulation of numerous fibrin strands at the site of injury. The thrombi thus formed also attract red blood cells and grows in size and can cause total occlusion of the vessel.

Implications of Ischemia

When the demand is not met due to critical occlusion various pathological, biochemical and electrophysiological alterations take place in the myocardial cell. All these changes usually occur at one particular vessel. Usually multiple vessels are not affected at the same time.

The segment that is affected causes that portion of myocardium to perform with decreased contractility or absent contractility or bulging or dyskinetic segment. All these ultimately lead to decrease in cardiac pump activity and cardiac output.

The sub endocardium is relatively receiving little blood supply when compared to the subepicardium. So even small occlusions in the sub endocardium cause great damage decreasing output function. Ultimately left ventricle failure can occur and papillary dysfunction and mitral regurgitation also happen as sequel. When these events happen transiently they cause angina. But total occlusion results in permanent scarring.

Treatment of dyslipidemia

The treatment of dyslipidemia is considered as the ultimate goal for freedom from angina, decreased necessity for revascularization, & decrease in incidence of cardiac ischemia and death. The regulation of lipids is reached by combining diet less in saturated and *trans*- fatty acids

work up, and losing weight. HMG-CoA reductase inhibitors are an indispensable part of treatment & can lessen LDL cholesterol (25–50%), increase high density lipoprotein cholesterol (5–9%) and lessen triglycerides (5–30%). Significant treatment effects due to statins on coronary events and outcome is achieved independent of the low density lipoprotein [36] level before treatment. Fibrates or niacin is given in order to increase high density lipoprotein levels & lessen triglycerides. Trials have shown that lipid lowering has benefited all classes of people.

The major issue is the patient compliance with these behavioral life style modifications and the physician often underestimates his role in motivating and educating patients to practice it not for days or months but lifelong. Patients also tend to discontinue treatment. The dropout rate is more than 50 % stressing upon patients education and motivation. It is the duty of the physician to ensure that patients come for constant follow up.

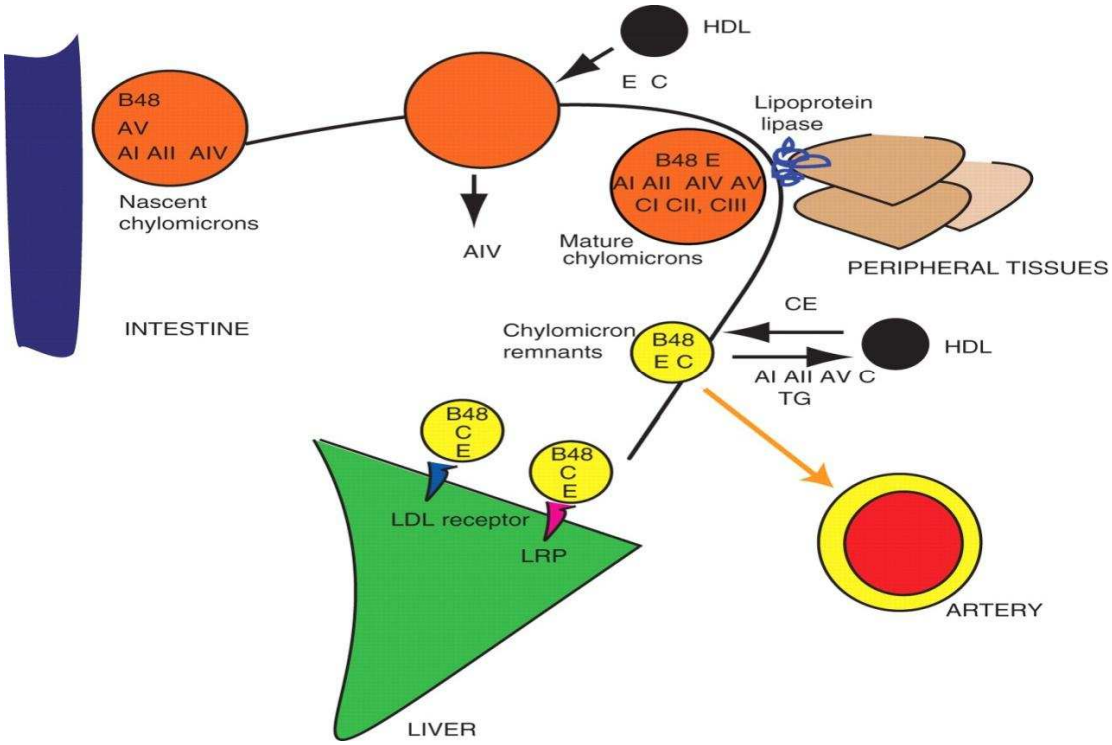
TREATMENT OF DYSLIPEDIMIA[39]

So considering the importance of dyslipidemia in increasing the life span of individuals worldwide many drug companies have invested much on this aspect of pharmacology. These drugs give benefit to individuals overall spectrum of cholesterol levels, mainly decreasing the low density lipoprotein values.

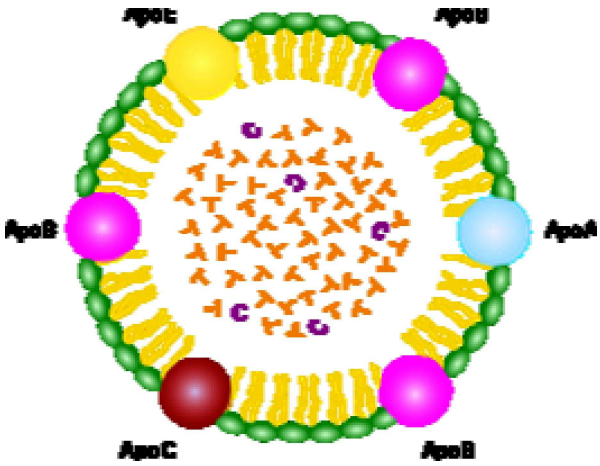
The Expert Panel 2002 recommends that the lipid modifying drugs should be initiated when an individual has less amount of blood HDL levels even though his LDL levels may not be high enough to achieve the target of starting lipid lowering therapy in the event of him having a risk factor .Heart Protection Study Collaborative Group study has indicated that starting drugs on patients with low HDL and average LDL has reduced the incidence of risk of CAD in in these patients by 30 %.

Plasma Lipoprotein Metabolism

Lipoproteins are molecules that have both lipids and proteins. The lipid constituents consist of free & esterified cholesterol & triglycerides and some include phospholipids also. The protein components are called Apo lipoproteins or shortly apoproteins. They give structural stability to the lipoproteins. They also serve as ligands when lipoprotein interacts with its receptors or serve as cofactors in enzymatic processes regulating metabolism of lipoproteins.



Chylomicrons



The body synthesizes chylomicrons by the absorption of triglycerides and cholesterol when absorption takes place after consumption of food from the small intestine.

This absorption of cholesterol and also various plant sterols from the intestine is achieved by the mediation of Niemann Pick like 1 protein thatis the place where the drug ezetimibe acts, which inhibits cholesterol absorption. Dietary cholesterol undergoes esterification with the help of the enzyme acyl coenzyme A (cholesterol acyltransferase) (ACAT). This enzyme is present in the intestine and in the liver the sites of esterification of free cholesterol before the assembly of lipoproteins rich in triglycerides take place. These are the chylomicrons & very-low-density lipoproteins.

The proportion of triglycerides and cholesterol is 10 or more. In patients with lipids within normal limits chylomicrons are found within plasma for three to 6 hours after ingestion of food rich in fat.

When the individual fasts for 10 to 12 hours chylomicrons disappear from the blood.

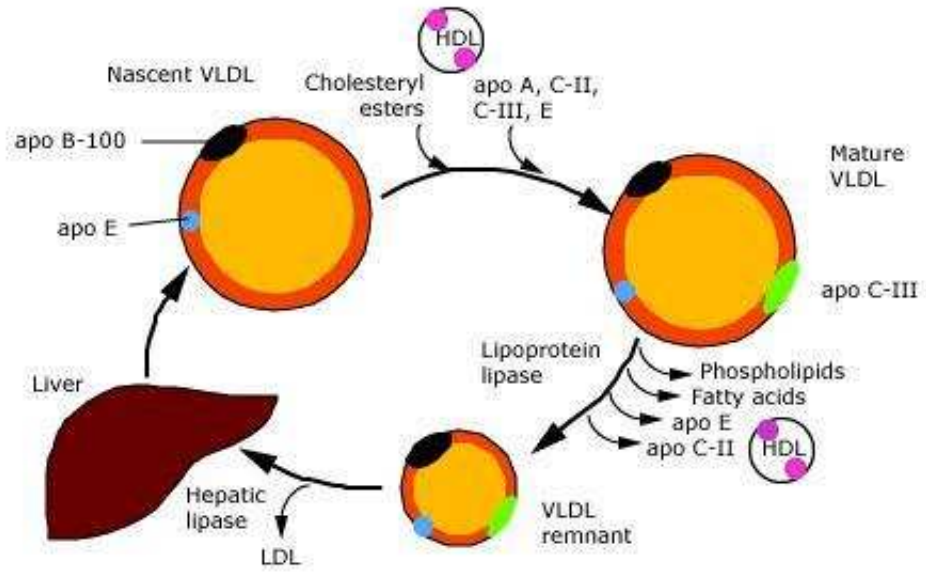
The apolipoproteins of chylomicrons consists of apoB-48, apoA-I, and apoA-IV. These are synthesized in the intestinal epithelial cells and few of them are derived from apoE and apoC-I C-II, and C-III when the chylomicrons are secreted into the lymph and enter the plasma.

Chylomicron Remnants

When the lipoprotein mediates the removal of the triglycerides from the chylomicrons, the remnants, have all of the remaining cholesterol obtained from food.

They remove themselves from the capillary surface and enter the liver and are removed by the liver with the help of Apo E.

Very-Low-Density Lipoproteins



When there is an increase in the flux of the free fatty acids in the liver or increased triglyceride content the liver decides to produce more very low density lipoproteins.

The size of these particles range between 40 to 100 nm in diameter & are large enough to lead to plasma turbidity. However unlike chylomicrons, these particles do not float spontaneously on the top of a tube containing undisturbed plasma.ApoB-100, apoE, and apoC-I, C-II, and C-III are synthesized by the liver cells and incorporated into VLDL. If triglycerides cannot synthesize VLDL, the newly synthesized apoB-100 is degraded by liver cells.

Low-Density Lipoproteins

The LDL particles are produced by the degradation of intermediate density lipoprotein. They have a t1/2 of 1.5 to 2 days. That is why they have more plasma concentration than VLDL and IDL. In Individuals not suffering from hypertriglyceridemia, 2/3rds of plasma cholesterol is present in low density lipoprotein cholesterol. ApoB-100 is the only Apo protein of LDL, and it is the ligand that binds Low density lipoprotein and its receptor molecule.

High-Density Lipoproteins

The metabolism of HDL is said to be complex because of the various process through which High density lipoprotein particles are altered in the compartment of plasma and by mechanism of synthesis of HDL. ApoA-I is the major HDL apoprotein, & its concentration in plasma is considered a good predictor of cardiovascular risk even better than high density lipoprotein cholesterol level.

Lipoprotein a

Lipoprotein a has a low density lipoprotein particle that has another Apo protein along with apoB-100.

	Targets			**Initiation of change in lifestyle**			**pharmacological Therapy Initiated for**		
RISK CATEGORY	**LDL-C**		**TC:HDL-C**	**LDL-C**		**TC:HDL-C**	**LDL-C**		**TC:HDL-C**
CHD or equivalent	<100	and	<3.5	100	or	3.5	100	or	3.5
2or more risk factors	<130	and	<4.5	130	or	4.5	130	or	6.0
0or1 risk factor	<160	and	<5.5	160	or	5.5	160	or	7.0

Guidelines Based on LDL-cholesterol and Total cholesterol: HDL-C Ratio for treating Low HDL-cholesterol Patients

Plasma lipid level classification	
Total cholesterol	
<200 mg/dl	Optimal
200–239 mg/dl	Slightly increased
240 mg/dl	High
High density lipoprotein	
<40 mg/dl	Low (<50 mg/dl for females)
>60 mg/dl	High
Low density lipoprotein	
<70 mg/dl	Ideal for high risk
<100 mg/dl	Ideal
100–129 mg/dl	Almost ideal
130–159 mg/dl	Slightly increased
160–189 mg/dl	High
190 mg/dl	significantly high
Triglycerides	
<150 mg/dl	Normal
150–199 mg/dl	Slightly increased
200–499 mg/dl	High
500 mg/dl	Significantly increased

STATIN THERAPY

The statins are the most effective drugs with less adverse events profile for treating patients suffering from dyslipidemia.

Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, by competitive inhibition which acts as a catalyst in an early, rate-limiting step in the synthesis of cholesterol.

Doses in the high range of the recent drugs with increased potency (*e.g.,* atorvastatin and simvastatin) also decrease triglyceride levels due to elevated VLDL levels.

Mechanism of action:

Statins cause reduction in cholesterol levels by decreasing synthesis of cholesterol by hepatocytes which causes increase in the expression of low density lipoprotein receptor gene. As free cholesterol content within hepatocytes is reduced, membrane bound SREBPs are cleaved by a protease and are trans located into nucleus. The transcription factors bind to the sterol responsive element of the low density lipoprotein receptor gene, increasing transcription & causing increase in the synthesis of low density lipoprotein receptors. Degradation of LDL receptors also is reduced.

Triglyceride Reduction by Statins

Triglyceride levels >250 mg/dl are brought down significantly by statins, & the % reduction achieved is like that of the % reduction in low density lipoprotein cholesterol. Similarly, hypertriglyceridemia occurring in patients who consume high doses of the best potency statins (simvastatin and atorvastatin, 80 mg/day; rosuvastatin, 40 mg/day) reach about 40% decrease in LDL-Cholesterol and also the same results are seen in triglyceride values.

Effects of Statins on HDL-C Levels

Many studies conducted for statin effectiveness have particularly eliminated HDL cholesterol levels. While analyzing patients with increased LDL-Cholesterol levels & near normal HDL Cholesterol values (40 to 50 mg/dl in males & 50 to 60 mg/dl in females), an elevation in HDL Cholesterol of 5 - 10% has been reported, in spite of the variations in the dose of statin employed.

But the case is not the same when the HDL cholesterol value is low. The reports are variable and need further study.

Potential beneficial effects apart from LDL lowering:

Statin treatment increases endothelial synthesis of nitric oxide which has beneficial action by causing vasodilatation.

Statins affects stability of plaque in many methods. Statins cause inhibition of monocyte entry into the site.

Statins decrease the coronary risk & high values of CRP which is considered an important marker for inflammation in spite of decreasing cholesterol.

Change in morphology of LDL by oxidation has a significant effect in affecting the uptake of lipoproteins by macrophages and also causing cytotoxic effects within lesions.

Statins decrease assembly and aggregation of platelets.

Bile Acid Sequestrants

The two well accepted bile acid sequestrants also widely called resins are cholestyramine & colestipol. They are the oldest among hypolipidemic class of drugs & they have safe adverse effect profile as they do not have their absorption at the small intestine. They can be used for patients between 11 to 20 years of age. As statins are good as monotherapeutic agents, they are commonly used as 2^{nd} line agents when statin therapy cannot attain its LDL lowering target successfully.

Niacin

Niacin (pyridine-3-carboxylic acid) is one of the age old dyslipidemic classes of drugs, which has its say on all lipid parameters. In fatty tissues, niacin decreases the lipolysis of triglycerides with the help of hormone sensitive lipase which decreases entry of free fatty acids into the liver and causes reduction of synthesis of triglycerides by the liver.

Fibric Acid Derivatives

Fibrates bind to PPAR which is expressed predominantly in the liver and brown adipose tissue & also to a certain degree in kidneys heart & skeletal muscle. Fibrates cause decrease in triglycerides by means of PPAR through increase in fatty acid oxidation increase in lipoprotein lipase synthesis and decrease in expression of lipoprotein lipase. Any increase in lipoprotein lipase levels will increase the removal of triglyceride rich lipoproteins.

Decrease in synthesis of apoC-III by the liver, acts by inhibiting lipolytic processing & receptor mediated clearance, will increase the removal of very low density lipoprotein. Fibrates mediated enhancement in HDL Cholesterol levels are because of PPAR stimulation of apoA-I and apoA-II expression, that enhances High density lipoprotein

cholesterol levels. Fenofibrate is more successful in increasing high density lipoprotein levels than gemfibrozil.

Ezetimibe and its inhibition of uptake of cholesterol from food

Ezetimibe is the 1st drug approved to decrease total and low density lipoprotein levels that decreases absorption of cholesterol by the intestinal enterocytes. It decreases low density lipoprotein levels by about 20 % and is used commonly as an add on therapy along with statins.

Non HDL cholesterol

It is calculated by deducting high density lipoprotein from total cholesterol. It includes VLDL, LDL, IDL ,VLDL remnants, chylomicron remnants and other remnant lipoproteins.

Significance

The decrease in coronary vascular risk by causing reduction in low-density lipoprotein cholesterol levels is widely accepted and low density lipoprotein Cholesterol is the ultimate goal in lipid lowering therapy. But this is not the case in all patients. Many patients do not have high LDL cholesterol levels. There is a increase in recognition of non-high density lipoprotein cholesterol as a significant predictor of cardiovascular risk. Non high density lipoprotein cholesterol can be

attained by deducting HDL cholesterol from total cholesterol and includes all components of cholesterol found within the atherogenic lipoprotein particle. Non HDL Cholesterol is very important in some subgroups, like those with diabetes, who are suffering from dyslipidemia which is marked by low HDL cholesterol levels & increased triglyceride levels. Measuring non HDL cholesterol is expected to capture the risk associated with triglyceride rich particles. Non HDL Cholesterol was found definitely to correlate with coronary artery disease severity and progression and also as a predictor of cardiovascular disease mortality. Treatments that target non HDL Cholesterol include lifestyle measures and drug therapy. Statins as a group except rosuvastatin and simvastatin do not significantly reduce non HDL cholesterol. Fibrates as a class of drugs have got significant role in decreasing triglycerides and non HDL Cholesterol. **Further non HDL Cholesterol is a calculated value using total cholesterol and HDL both of which are got from direct measurements whereas LDL cholesterol is a predicted value using FRIEDWALDS equation. Non HDL cholesterol includes all the atherogenic particles in the lipid profile. Hence its considered to have a superior predictive value.**

National cholesterol education program

LDL & Non High density lipoprotein Goals for3 Risk subdivisions

Risk subcategory	LDL target	Non-HDL target
Coronary risk equivalent, diabetes included	<100mg/dl	<130mg/dl
Two or more Risk Factors	<130mg/dl	<160mg/dl
0 or 1RiskFactor	<160mg/dl	<190mg/dl

Non HDL Cholesterol levels & cardiovascular Risk assessment

Numerous trials conclude that a strong relationship exists between non HDL Cholesterol and atherosclerosis, even in youth. When autopsy was conducted in young deaths and analysed it was concluded that non HDL Cholesterol was related to the presence of fatty streaks and elevated lesions in the coronary arteries. It was proved that there was strong relationship between the degree of atherosclerosis & HDL cholesterol levels and non-high density lipoproteins.

The Cholesterol Lowering Atherosclerosis Study which was done 15 years ago undoubtedly established a clear association between non HDL and coronary vascular disease risk. This was a randomized placebo-controlled trial of colestipol along with niacin treatment in males who had prior coronary bypass surgery. This study concluded that, non HDL Cholesterol was undoubtedly the best predictor of all the changes in

degrees of coronary disease in males who were not on treatment with medications to lower cholesterol. Another study named as “The Lipid Research Clinics Follow-up Study” was done to analyse if non HDL Cholesterol predicted cardiovascular disease mortality in older age groups (40 to 64 years) who did not suffer from coronary artery disease at baseline. It concluded that in men both LDL-C and non–HDL-C had same predictive values while in females non–HDL-Cholesterol was a better predictor.

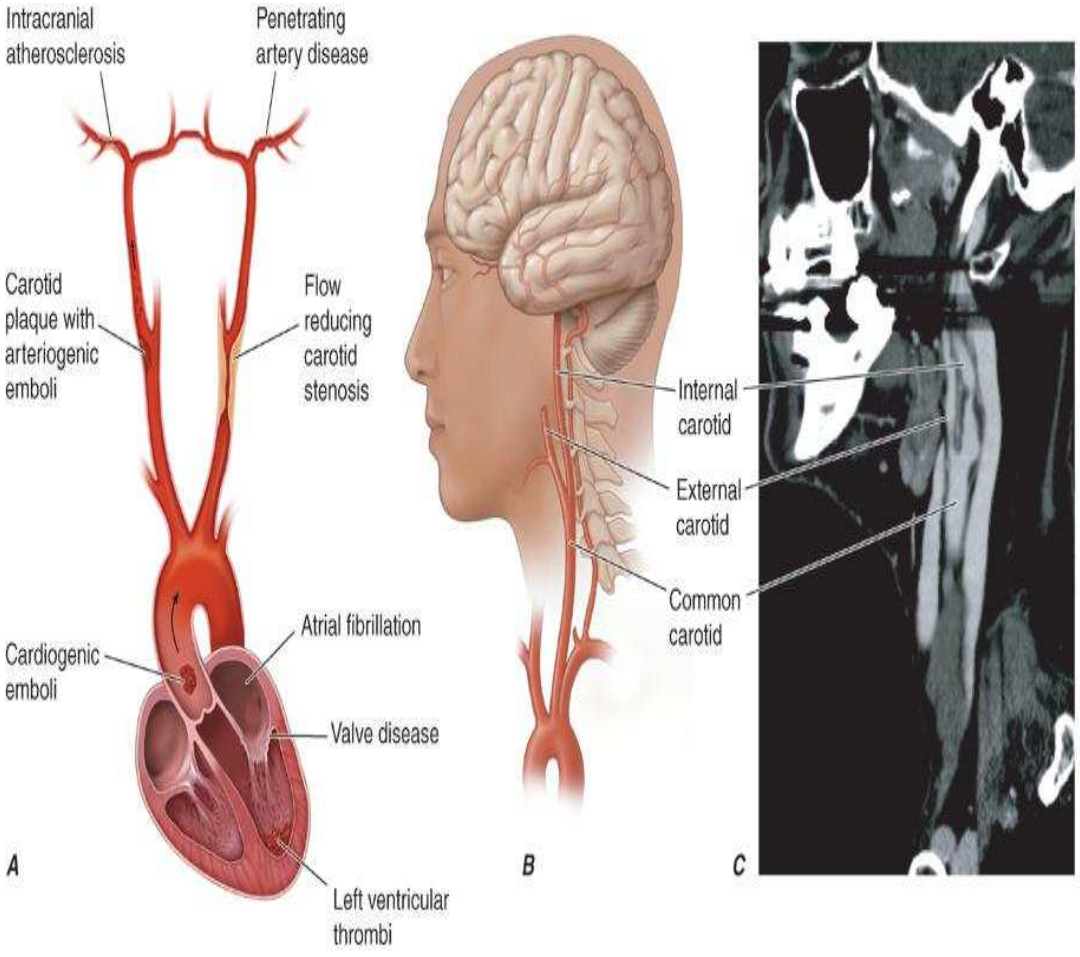
“*Non-HDL cholesterol is a surrogate marker for all the major atherogenic lipoproteins.”*

In order to state otherwise, non-high density lipoprotein cholesterol may be a better predictor of cardiovascular risk than low density lipoprotein cholesterol or triglycerides in certain patient populations, since it reflects the total serum cholesterol carried by all of the potentially atherogenic lipoproteins— LDL, VLDL, IDL, Chylomicron remnants and other remnant lipoproteins. And also as it is calculated from total cholesterol and high density lipoprotein cholesterol, both of which are got by direct measurements. It does not get affected by the triglyceride level and we need not collect the specimen in fasting.

CEREBROVASCULAR ACCIDENT

The common terminology is the *stroke*, defined as the sudden onset of a non convulsive, focal neurologic deficit.

PATHOPHYSIOLOGY OF ISCHEMIC STROKE



A. Diagram to demonstrate the 3 major mechanisms responsible for ischemic stroke:

1. An intracranial artery occluded because of an embolus that has its origin at a distant site. Examples are cardiogenic sources such as atrial fibrillation or artery-to-artery emboli from carotid atherosclerotic plaque, most commonly occluding larger intracranial vessels
2. In situ thrombosis of an intracranial vessel, typically affecting the small penetrating arteries that arise from the major intracranial arteries
3. Hypoperfusion due to flow-limiting stenosis of a major extracranial (e.g., internal carotid) or intracranial vessel, commonly causing “watershed” ischemia.

B and C. Diagram and reformatted CT angiogram of the common, internal, and external carotid arteries. High-grade stenosis of the internal carotid artery, which may be associated with either cerebral emboli or flow-limiting ischemia,

PHYSIOLOGY

The adult brain, measures around 1500 g or 2% of the total body weight, and needs about 150 g of glucose and 72 L of oxygen every 24 hours without any interruption.

This amounts to 20% of the body’s total oxygen consumption. Since the brain cannot store the substances, severe affect in functioning occurs after only a few minutes of absence of either the oxygen or

glucose or their reduction below critical levels. At rest, each cardiac contraction gives about seventy millilitre of blood into the ascending aorta. Ten to fifteen mL is provided to the brain. Every minute, about 350 mL flows through each internal carotid artery, and 100 to 200 mL through the vertebra basilar system, to achieve a total cerebral blood flow of 50 mL/min per 100 g.

Features

Premonitory stroke symptoms are not always found; fewer than 20% of stroke patients have a prior TIA. Focal premonitory symptoms, when present, usually predate infarction rather than haemorrhage.

When they occur, they may be so nonspecific that they are not recognized as signs of an impending stroke. Within 90 days after a TIA, the risk of stroke has been reported to be as high as 10% to 20%, and nearly half of these patients will have their stroke in the first 2 days after the TIA.

"Risk factors for stroke"

			Number Needed to Treat[a]	
Risk Factor	**Relative Risk**	**Relative Risk Reduction with Treatment**	**Primary Prevention**	**Secondary Prevention**
Hypertension	2–5	38%	100–300	50–100
Atrial fibrillation	1.8–2.9	68% warfarin, 21% aspirin	20–83	13
Diabetes	1.8–6	No proven effect		
Smoking	1.8	50% at 1 year, baseline risk at 5 years' postcessation		
Hyperlipidemia	1.8–2.6	16–30%	560	230
Asymptomatic carotid stenosis	2.0	53%	85	N/A
Symptomatic carotid stenosis (70–99%)		65% at 2 years	N/A	12
Symptomatic carotid stenosis (50–69%)		29% at 5 years	N/A	77

Risk factors for ischemic stroke

Modifiable and non-modifiable risk factors for ischemic stroke have been identified and include age; gender; race/ethnicity; heredity; hypertension; cardiac disease, particularly atrial fibrillation; diabetes mellitus; hypercholesterolemia; cigarette smoking; and alcohol abuse, hypercoagulable states and patent foramen ovale.

Brain Infarction[17]

Brain or neuronal dysfunction occurs at cerebral blood flow levels of below 50 mg/dL, and irreversible neuronal injury is initiated at levels below 30 mg/dL. Both the degree and duration of reductions in cerebral blood flow are related to the likelihood of sustained neuronal injury.

When blood supply is completely interrupted for 30 seconds, brain metabolism is altered. After 1 minute, neuronal function may cease. After 5 minutes of interruption, anoxia initiates a chain of events that may result in cerebral infarction; however, if oxygenated blood flow is restored quickly enough, the damage may be reversible, as with a TIA. The following steps occur in the evolution of an infarct: (1) local vasodilatation and (2) stasis of the blood column, with segmentation of the red cells, followed by (3) oedema and (4) necrosis of brain tissue. The earliest ischemic changes are visualized by increased water content in diffusion-weighted MRI while with time, an infarct is well delineated by fluid-attenuated inversion recovery (FLAIR) and T2-weighted changes on MRI.

Large-vessel Atherosclerotic Infarction

Atherosclerotic plaque that occurs at the site of a bifurcation in any of the larger vessels will cause stenosis progressively, as the final large artery occlusion is because of thrombosis in the lumen that is narrowed. Arteriosclerotic plaques can originate at any site along the carotid artery & the vertebrobasilar system. Yet the most common sites are the bifurcation of the common carotid artery into the external and internal carotid arteries, the origins of the middle and anterior cerebral arteries, and the origins of the vertebral from the subclavian arteries.

An atherosclerotic stenosis or occlusion may also lead to a cerebral infarction through an embolic mechanism. In this case, emboli arising from the proximally situated atheromatous lesions occlude otherwise healthy branches located more distally in the arterial tree.

Small-Vessel Lacunar Infarction

This particular subtype has various named entities, because of ischemia confined to the territory of a single vessel. They reflect arterial disease of penetrating vessels which supply the internal capsule, basal ganglia, thalamus, corona radiata, and paramedian regions of the brainstem. Disagreements exist about the pathogenesis of lacunar infarcts; some studies consider the use of the term lacunae to describe size and location, without indicating a specific pathology. The pathologies of only a handful of such infarcts have been studied by serial section, and only a few of those studies have documented a tiny focus of microatheroma or lipohyalinosis stenosing one of the deep penetrating arteries. The arterial damage is generally due to long-standing hypertension or diabetes mellitus.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study was done in Mahatma Gandhi Memorial Government hospital from the period of May 2010 to December 2012.

Consent was obtained from all participants

Inclusion criteria

Patients on established coronary artery disease who were on atorvastatin therapy 10 mg for more than 1 year, who developed an ischemic stroke evidenced by CT scan or MRI within 5 years of occurrence of the first coronary event.

Exclusion criteria

Age less than 40 years.

Patients on irregular statin therapy.

Patients with chronic kidney disease.

Patients with chronic liver disease

Patients who had poor left ventricle function

STUDY DESIGN

Number of study groups : two

Group 1 CASES: 50 patients with a history of coronary artery disease with ECG or ECHO confirmation and who were on regular atorvastatin therapy 10 mg daily for more than one year who developed a cerebrovascular event in the form of ischemic stroke with CT or MRI Brain evidence within 5 years of occurrence of the first coronary event were included in the study.

Group 2 CONTROLS: A suitable control of 50 patients matching age, sex, smoking, alcohol and diabetes who had coronary artery disease and were also on atorvastatin therapy 10 mg for more than 5 years were included. These patients should have normal CT brain and no prior history suggestive of transient ischemic attacks.

Study size: 50

Study type: case control study

The age ranges from 40 to 80 and the study included both sexes. The study was approved by institutional ethics committee. The risk factors associated with, both modifiable like cigarette smoking, alcohol consumption, hypertension, diabetes mellitus and obesity (BMI) and non-modifiable like age, sex, family history was taken into consideration. The risk factors smoking and alcohol were found out by careful history taking.

The risk factors DM and HT were detected by past medical history and laboratory routine investigation and BP measurement.

Total cholesterol HDL Cholesterol and triglycerides were measured in overnight fasting of 10 hrs. at 7 a.m. in the morning using Hitachi 704 Analyser . Low density lipoprotein Cholesterol was calculated by the FRIEDWALD formula LDL-chol = total chol - HDL-chol - Triglycerides/5 which is internationally accepted. Non HDL cholesterol was calculated by deducting HDL from total cholesterol. Both cases& controls were established coronary artery disease with ECG and ECHO confirmation.

All the basic blood investigations were done and their body mass index was calculated and the presence of metabolic syndrome was analysed. Those who had elevated renal parameters or abnormal liver function tests were excluded from the study.

Statistical analysis

Descriptive statistics were used to calculate the frequency, mean, median, and standard deviation. For all normally distributed variables, unpaired t test was used to determine the significant mean difference in groups. Chi squared test was used to compare discrete variables.

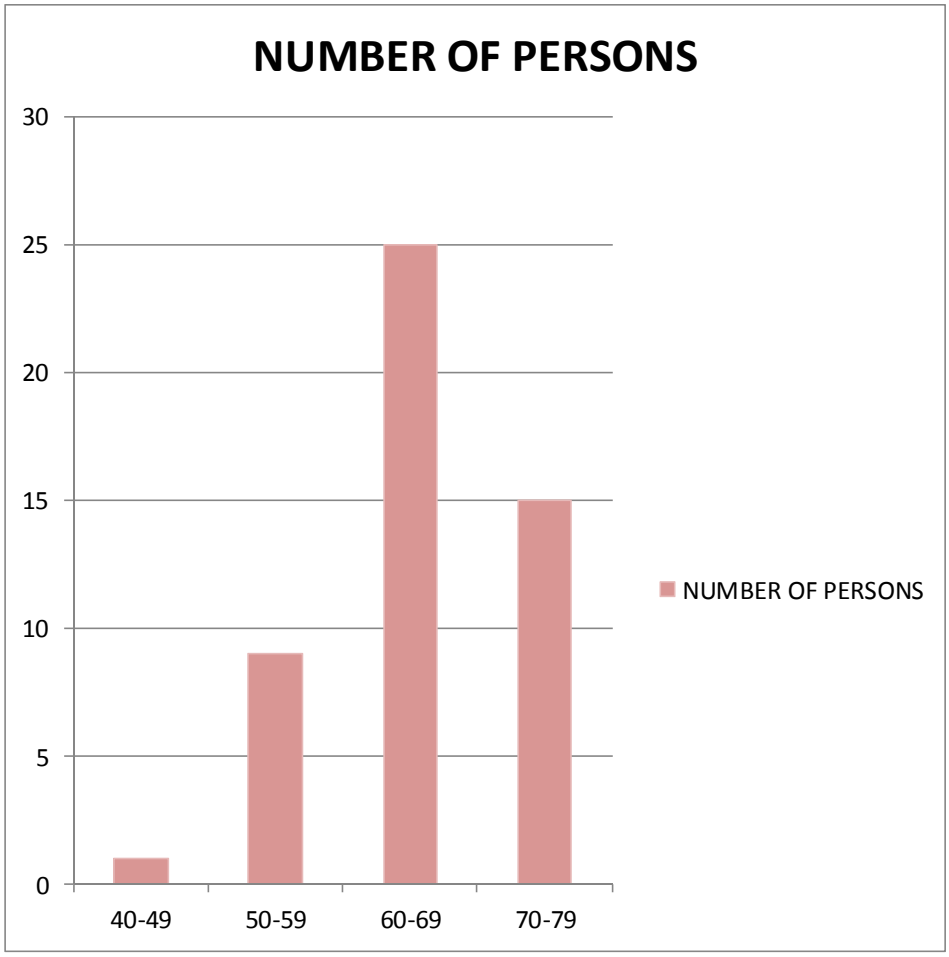
RESULTS AND ANALYSIS

RESULTS AND ANALYSIS

50 patients with a history suggestive of coronary artery disease with ECG or ECHO confirmation and who were on regular atorvastatin therapy 10 mg for more than one year who developed a cerebrovascular event in the form of ischemic stroke with CT or MRI Brain within 5 years of the occurrence of the first coronary event were included in the study. A suitable control of 50 patients eliminating age, smoking, diabetes, hypertension, alcohol consumption were included.

Age

AGE RANGE	**NUMBER OF PERSONS**
40-49	1
50-59	9
60-69	25
70-79	15
TOTAL	50



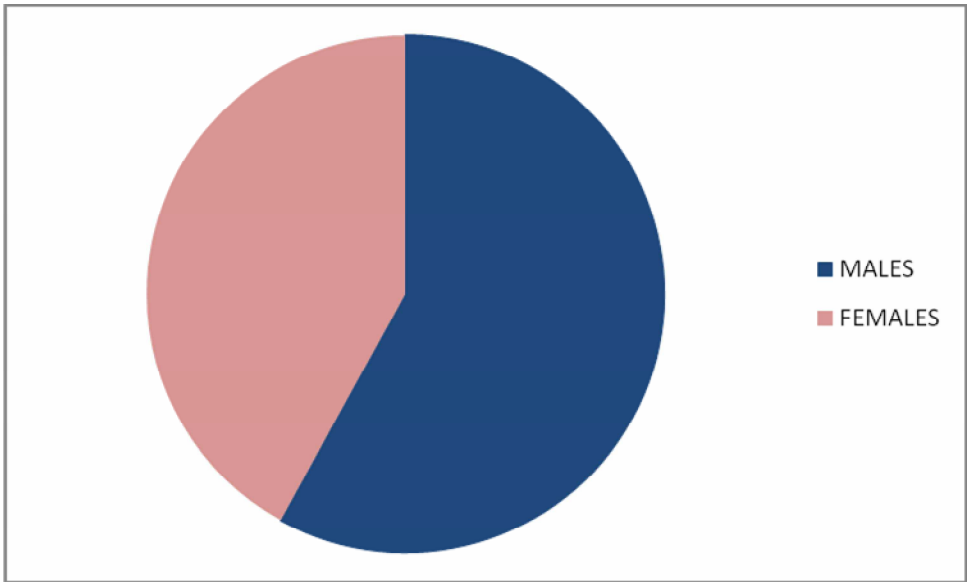
Age distribution

In our study the mean age of the population was 66.4 years .The majority of patients (25) in our study were in the age group 60 to 69 years.

Sex

SEX	No. OF CASES
MALES	29
FEMALES	21
TOTAL	50

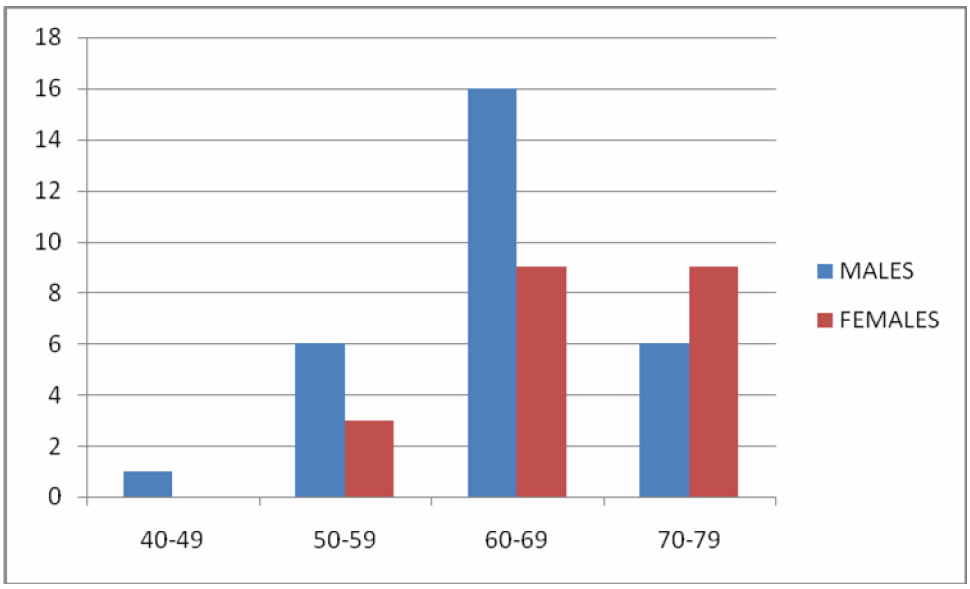
Sex distribution



Out of the 50 cases 29 were males and 21 were females.

AGE SEX RATIO

AGE	MALES	FEMALES	RATIO
40-49	1	O	0% female
50-59	6	3	50% FEMALE
60-69	16	9	56.25% FEMALE
70-79	6	9	150 %FEMALES
TOTAL	29	21	



Age sex ratio

The age sex ratio indicates that females had later onset of vascular events compared to males

There were 29 males & 21 females. Their average age was 67.72 years; females were somewhat elder to their male counterparts. Most of

them belonged to the 60-69 years age group (50%). Youngest male was a 45 years old electrician, who had hyper homo cystinemia. He also had evidence of peripheral arterial disease. He had strong family history of Coronary and cerebro vascular disease.

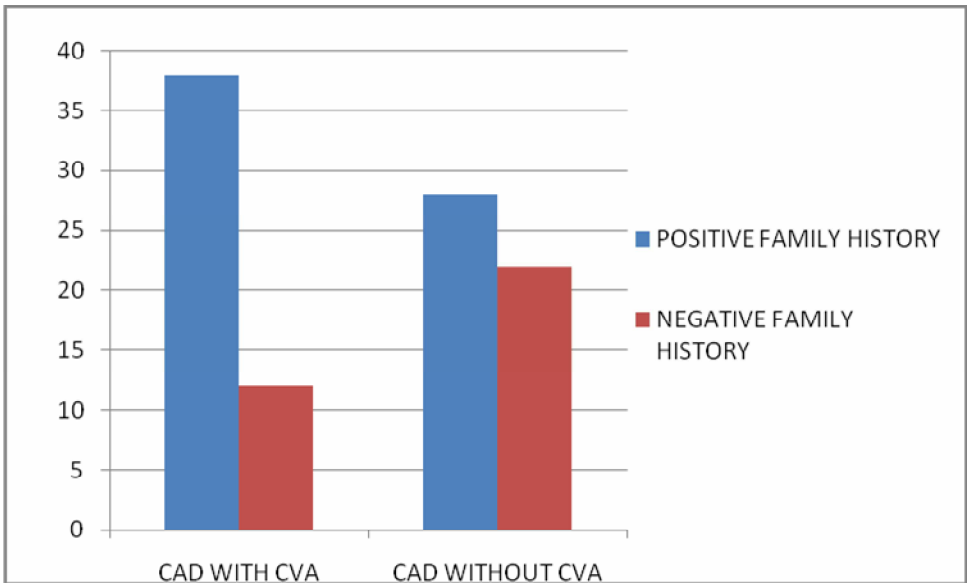
FAMILY HISTORY

In our study 38 (74%) CAD patients who developed CVA had positive history of ischemic events in family and 28 (56%) of the controls who were CAD patients and did not develop CVA had positive family history. Chi squared equals 8.117 with 1 degrees of freedom.

The two-tailed P value equals 0.0044

By conventional criteria, this difference is considered to be very statistically significant.

	CAD WITH CVA	**CAD WITHOUT CVA**
+ FAMILY HISTORY	38	28
no FAMILY HISTORY	12	22



$$\text{RelativeRisk} = \frac{\text{Incidence of CAD with CVA in patients with family history}}{\text{Incidence of CAD with CVA in patients with negative history}}$$

$$= a/(a+b) \div c/(c+d)$$

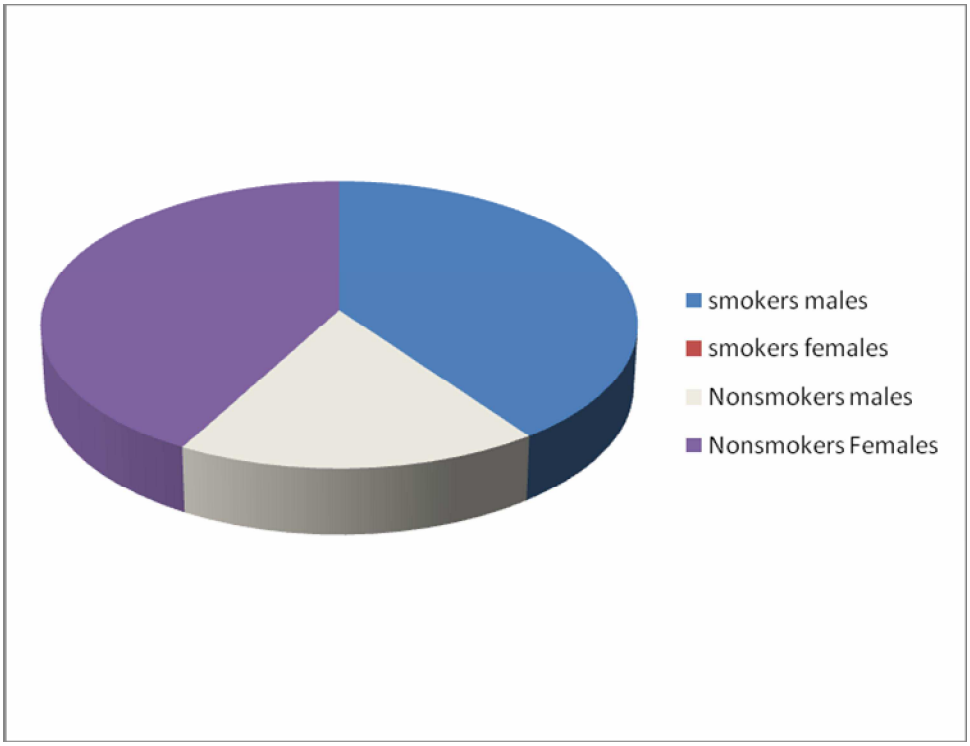
$$= \mathbf{1.6}$$

Thus a positive family history can be associated with a 1.6 fold increase in the risk of developing CVA in established CAD patients.

It is important to remember that earlier onset of both coronary and cerebrovascular events were observed in patients with positive family history.

Smoking

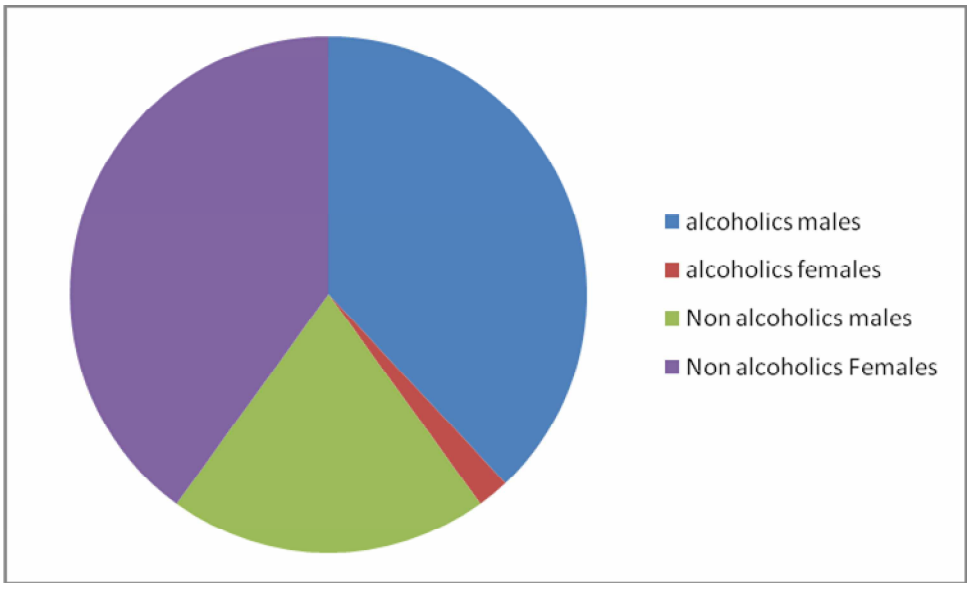
Total	**Smokers**		**Nonsmokers**	
50	males	females	males	Females
	20	0	9	21



Out of the 50 patients 20 were smokers which accounts to 40 %.All the 21 females were nonsmokers. But 17 of the females were exposed to passive smoking.

Alcoholism

Total	Alcoholics		Non alcoholics	
	Males	females	males	Females
	19	1	10	20

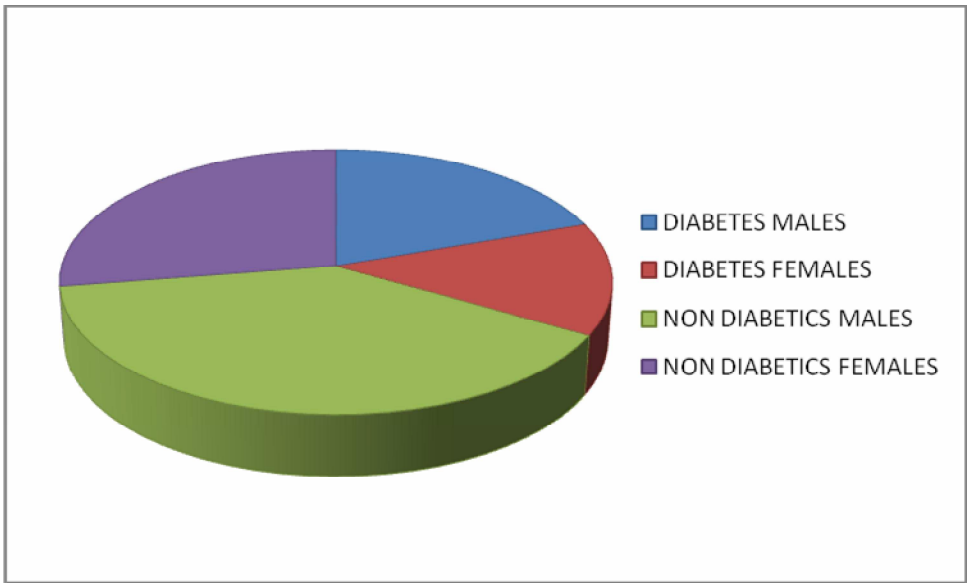


Out of the 50 patients 20 were alcoholics which accounts to 40 %. Out of the 21 females one was an alcoholic. She works as a cleaner in a bar shop and developed the habit of tasting the left over wines and became addicted to it.

The controls were matched for smoking and alcoholic. Except that the lone female alcoholic could not be suitably matched.

DIABETES MELLITUS

	DIABETES		**NON DIABETICS**	
50	MALES	FEMALES	MALES	FEMALES
	10	6	19	15
TOTAL	16		34	



Out of the 50 patients studied 16 were known diabetes patients on treatment accounting to 32% of cases.

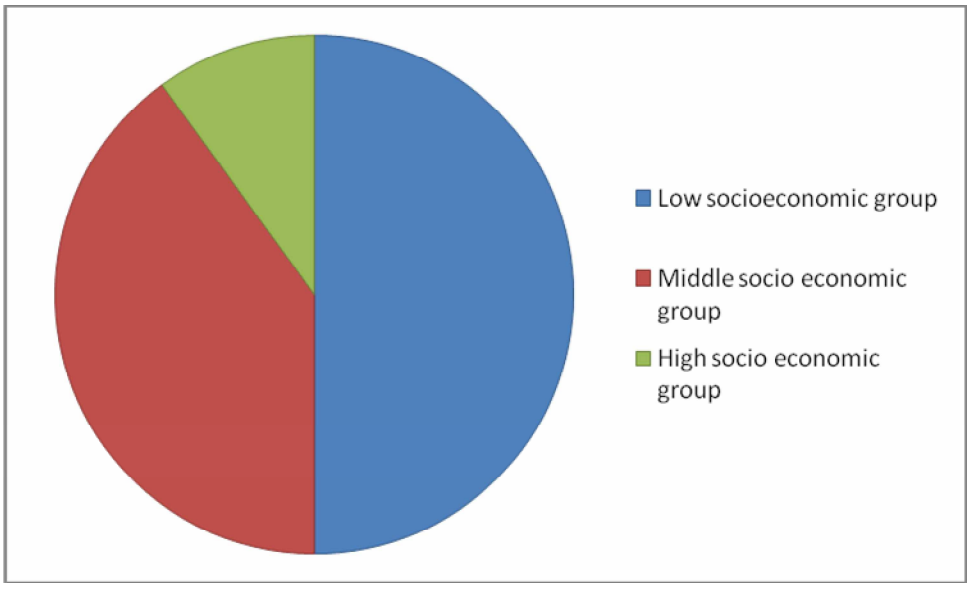
The controls were matched for diabetes.

SOCIO ECONOMIC STATUS

50% of patients belonged to lower socio economic group, while 40% were from middle income group and only 10% were from upper group.

Existence of coronary artery disease in the lower socio economic group of people in the urban areas has changed considerably due to change in lifestyle. The more number of patients in low socio economic group could be because of more number of low socio economic group people visiting government hospital in general.

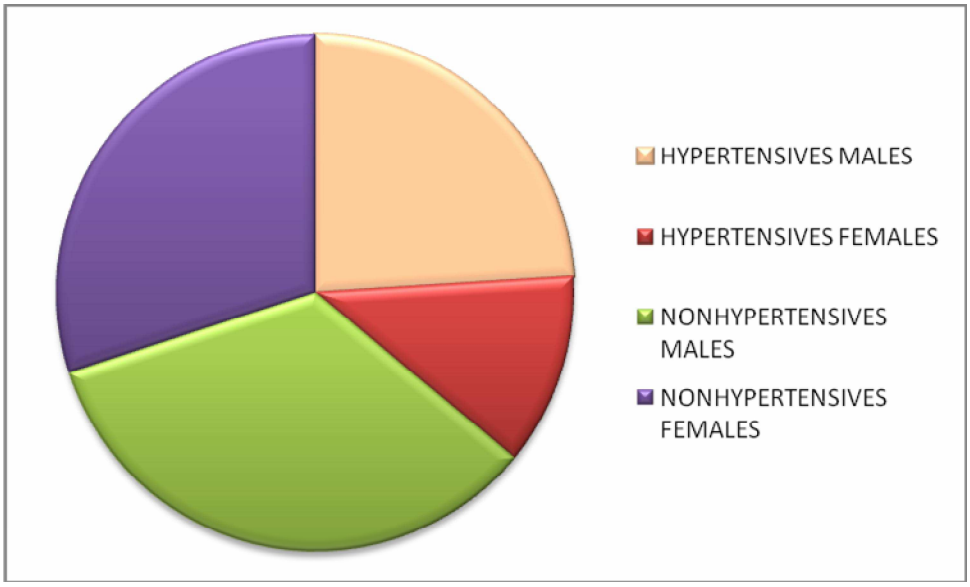
Low socioeconomic group	Middle socio economic group	High socio economic group
25	20	5



HYPERTENISON

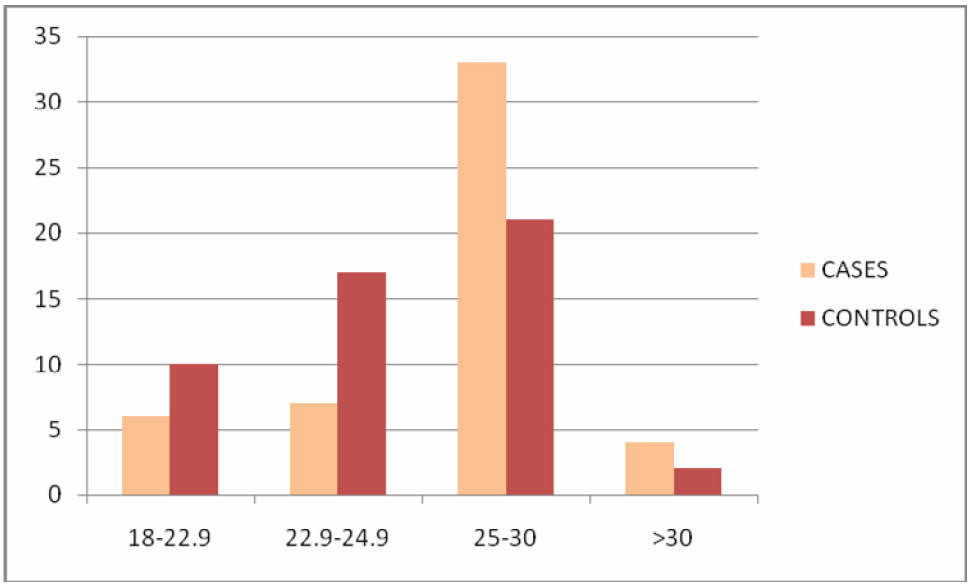
Out of the 50 patients 36% were hypertensive. The controls were matched for hypertension.

TOTAL	**HYPERTENSIVES**		**NONHYPERTENSIVES**	
	MALES	FEMALES	MALES	FEMALES
	12	6	17	15
TOTAL	18		32	



BODY MASS INDEX

	CASES	CONTROLS
18-22.9	6	10
22.9-24.9	7	17
25-30	33	21
>30	4	2
TOTAL	50	50



The Body mass index was calculated by the formula

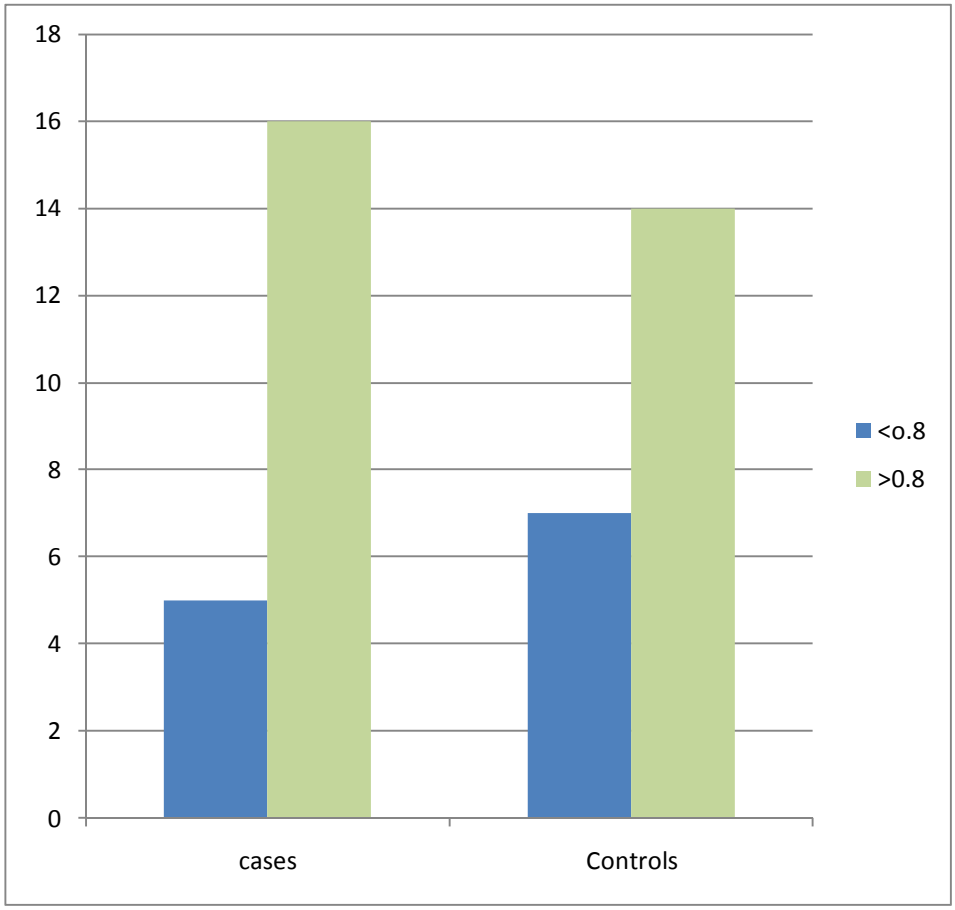
Weight in kg divided by height in cm squares

Normal	18.5 - 22.9
Overweight	23.0 - 24.9
Obese	=>25.0

88 % of cases and 80 % of controls were having a higher than normal BMI. The results showed that with increasing obesity the prevalence of multiple ischemic events was increasing. An increase in BMI with increasing age was observed. The average BMI among cases was 27.03. SD was 3.42. Average BMI among controls was 25.4. SD was 2.97. The p value was 0.0125 which is considered statistically significant. There was high prevalence of sedentary life style and faulty eating habits. Since both the cases and controls were on atorvastatin therapy they had the wide spread belief that they can adopt these faulty habits. Proper counselling was given to all the 100 patients included in the study.

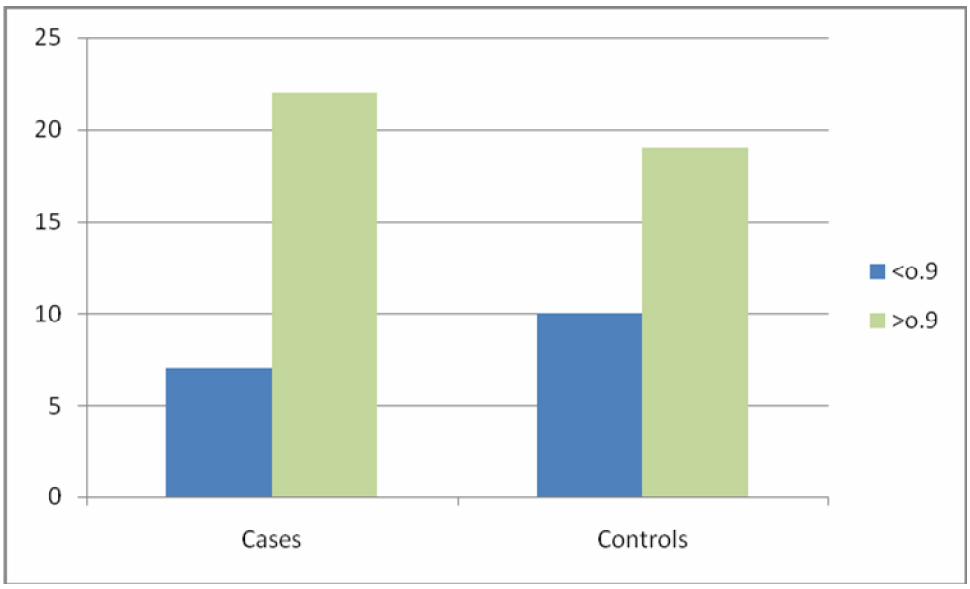
Waist hip ratio in women

In women	Cases	Controls
<o.8	5	7
>0.8	16	14
Total	21	21



Waist hip ratio in men

In men	Cases	Controls
<o.9	7	10
>o.9	22	19
Total	29	29



66.6 % of women and 75.8% of men were having a higher than normal waist circumference.

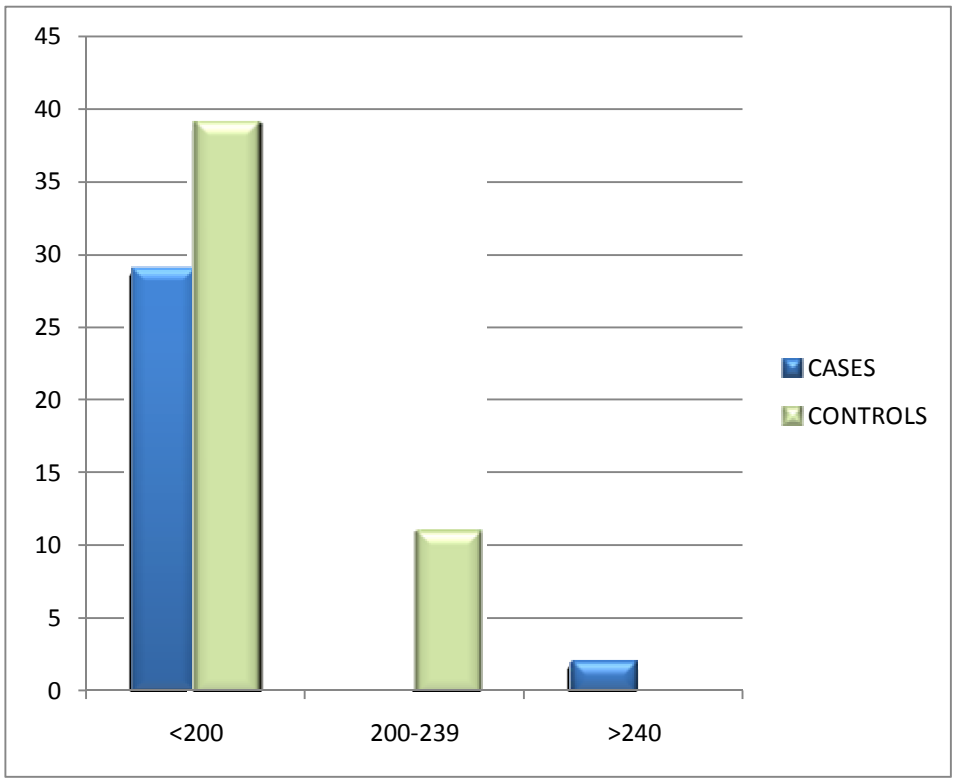
SERUM LIPID PROFILE

Total cholesterol HDL Cholesterol and triglycerides were measured in overnight fasting of 10 hrs at 7 a.m in the morning using Hitachi 704 Analyzer. LDL Cholesterol was calculated by using the Freidwald's formula LDL cholesterol = total chol - [High density lipoprotein cholesterol - Triglycerides/5 which is internationally accepted. Non HDL cholesterol was calculated by deducting HDL cholesterol from total cholesterol.

TRENDS IN TOTAL CHOLESTEROL

"Total Cholesterol	division
< 200	good
200 - 239	slightly High
>=240	High"

TOTAL CHOL	CASES	CONTROLS
<200	29	39
200-239	19	11
>240	2	0
TOTAL	50	50



TOTAL CHOLESTEROL

Total cholesterol

58 % of cases 78 % of controls had their total cholesterol within optimal levels. The mean total cholesterol among cases was 197.14 mg/dl. The mean total cholesterol among controls was 180.34 mg/dl.The effect of statins on reducing the total cholesterol was evident.

Unpaired t test results

P value and statistical significance:

The two-tailed P value equals 0.0050. By conventional criteria, this difference is considered to be very statistically significant**.**

Confidence interval:

The mean of Group One minus Group Two equals 16.8000.

95% confidence interval of this difference: From 5.2030 to 28.3970

Intermediate values used in calculations:

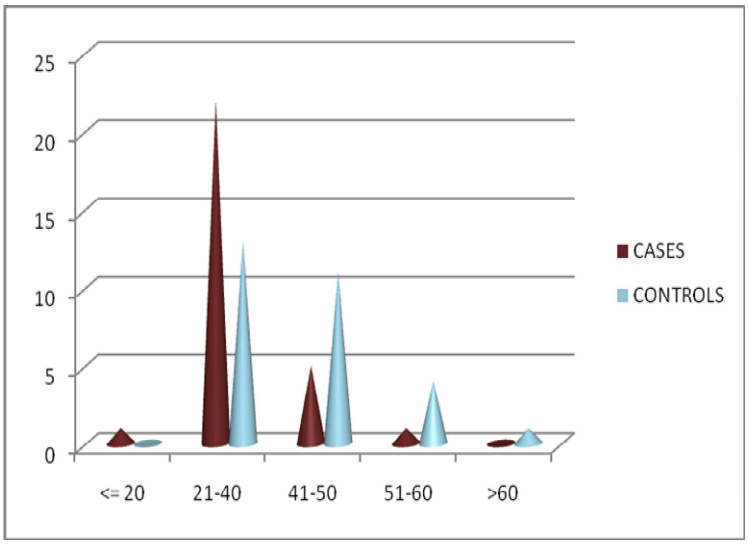
t = 2.8748: df = 98. standard error of difference = 5.844

Group	CASES	CONTROLS
Mean	197.1400	180.3400
SD	36.0600	20.1800
SEM	5.0997	2.8539
N	50	50

HDL CHOLESTEROL IN MEN

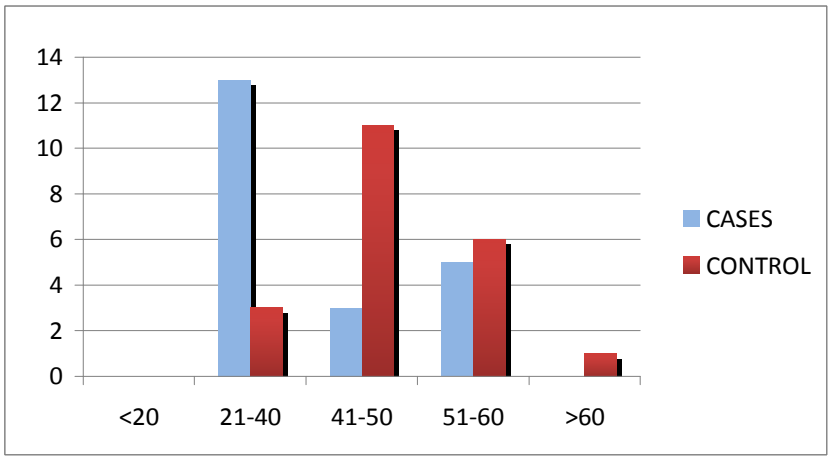
HDL cholesterol in men

MEN HDL	CASES	CONTROLS
<= 20	**1**	**0**
21-40	**22**	**13**
41-50	**5**	**11**
51-60	**1**	**4**
>60	**0**	**1**
TOTAL	**29**	**29**



79.3% of cases and 44.8% of controls had HDL<40 which is considered as a significant value for the development of atherosclerosis.

Women HDL	**CASES**	**CONTROL**
<20	0	0
21-40	13	3
41-50	3	11
51-60	5	6
>60	0	1
TOTAL	21	21



HDL CHOLESTEROL IN WOMEN

76.1 % of women cases and 66.6 % of controls had significantly low HDL cholesterol**.**

The mean HDL cholesterol among (both men and women) cases was 37.6 mg/dl. The mean HDL cholesterol among controls was 44.4 mg/dl. UNPAIRED T TEST RESULTS:

P value and statistical significance:

The two-tailed P value is less than 0.0001

This difference is extremely statistically significant. Confidence interval: The mean of Group One minus Group Two equals -6.6000 95% confidence interval of this difference: From -9.7602 to -3.4398 Intermediate values used in calculations:

t = 4.1445:df = 98: standard error of difference = 1.592

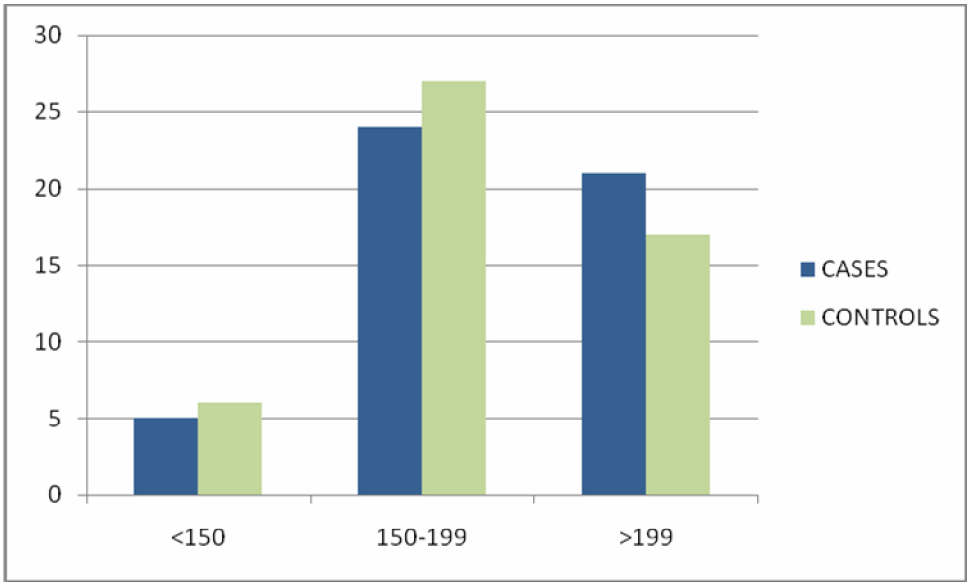
Group	CASES	CONTROLS
Mean	37.1000	43.7000
SD	8.1500	7.7700
SEM	1.1526	1.0988
N	50	50

TRENDS IN TRIGLYCERIDES

“Triglyceride	DIVISION
< 150	WITHIN normal limits
150 - 199	Slightly more
200 - 499	Higher
>=500	significantly high”

TGL	CASES	CONTROLS
<150	5	6
150-199	24	27
>199	21	17
Total	50	50

Triglycerides



Only 10 % of cases and 12 % of controls had optimal triglyceride levels. The results indicate that statins did not help much in reducing triglycerides in the population studied.

The mean triglycerides among cases were 194.4mg/dl. The mean triglycerides among controls was 190mg/dl

Unpaired t test results

P value and statistical significance: The two-tailed P value equals 0.5444.This difference is considered to be not statistically significant.

Confidence interval: The mean of Group One minus Group Two equals 3.5600. 95% confidence interval of this difference: From -8.0553 to 15.1753 .Intermediate values used in calculations:

t = 0.6082:df = 98: standard error of difference = 5.853

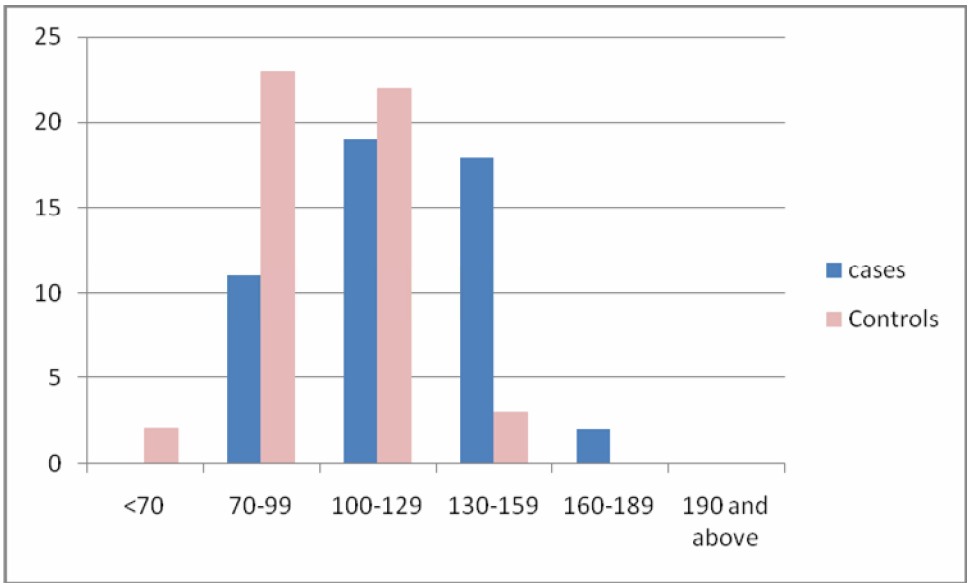
Group	CASES	CONTROLS
Mean	193.1600	189.6000
SD	30.5700	27.9000
SEM	4.3233	3.9457
N	50	50

TRENDS IN VLDL

The average VLDL among cases was 38.8mg/dl. The average VLDL among controls was 30mg/dl. Since VLDL was calculated from triglycerides test of significance was not applied .

TRENDS IN LDL

LDL	Cases	Controls
<70	0	2
70-99	11	23
100-129	19	22
130-159	18	3
160-189	2	0
190 and above	0	0
total	50	50



LDL cholesterol

"LDL <70	Goal LDL for CAD patients
< 100	Good
100 - 129	Almost good, borderline good
130 - 159	Borderline more
160 - 189	Higher
>=190	significantly high"

LDL CHOLESTEROL

22% of cases and 46% of controls had their LDL cholesterol within optimal results. Only 4 % of controls had reached the target LDL value. Since both cases and controls were on regular atorvastatin therapy levels the LDL levels of many patients were near optimal levels. The mean LDL cholesterol among cases was 121.34 mg/dl. The average LDL Cholesterol among controls was 98.72 mg/dl.

P value and statistical significance: . The two-tailed P value is less than 0.0001: This is considered to be extremely statistically significant.

Confidence interval:

The mean of Group One minus Group Two equals 22.6200

95% confidence interval of this difference: From 12.5598 to 32.6802.

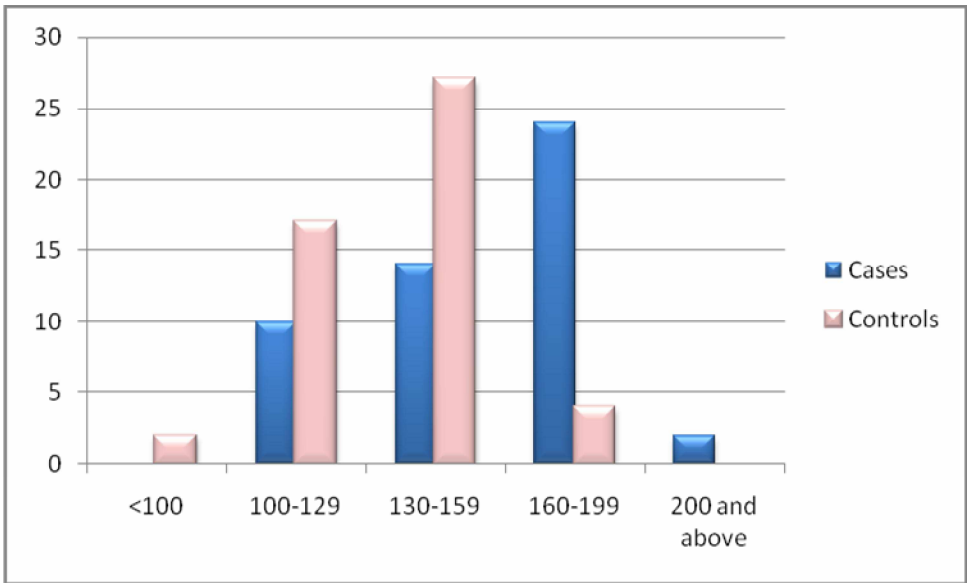
Intermediate values used in calculations:

t = 4.4620:df = 98: standard error of difference = 5.069.

Group	CASES	CONTROLS
Mean	121.3400	98.7200
SD	27.9300	22.4700
SEM	3.9499	3.1777
N	50	50

THE NON HDL CHOLESTEROL

NON HDL	Cases	Controls
<100	0	2
100-129	10	17
130-159	14	27
160-199	24	4
200 and above	2	0
total	50	50



non HDL cholesterol

Non HDL cholesterol

The cut off for non HDL cholesterol is generally thirty mg/dl more than LDL cut off values. 38 % of controls had their non-high density lipoprotein cholesterol in the optimal range. But only 20 % of cases had

their non HDL cholesterol in the optimal range. The mean non HDL cholesterol among cases is 160.04 mg/dl. The mean HDL cholesterol among controls is 136.64 mg/dl.

Unpaired t test results

P value and statistical significance: The two-tailed P value is less than 0.0001: By conventional criteria, this difference is considered to be extremely statistically significant. The mean of cases minus controls equals 23.4. 95% confidence interval of this difference: From 13.5500 to 33.2500. Intermediate values used in calculations:

t = 4.7144:df = 98: standard error of difference = 4.964 d *t* test results

Group	cases	controls
Mean	160.0400	136.6400
SD	28.3800	20.6500
SEM	4.0135	2.9204
N	50	50

This indicates that the difference in non HDL cholesterol contributed significantly in the occurrence of a second ischemic event in the form of cerebrovascular accident in the study population. Despite statin therapy the difference in non HDL cholesterol remains a significant contributing factor in the development of cerebrovascular accident.

DISCUSSION

DISCUSSION

Why atorvastatin was chosen?

It is one of the most commonly prescribed lipid lowering drug in our hospital. The most common side effects are hepatotoxicity and myopathy. Its beneficial effects include lowering LDL , and triglycerides to a certain extent. So the patients on atorvastatin are likely to have less LDL cholesterol values than the general population.It does not cause significant increase in HDL like that of rosuvastatin. Hence it has little effect in altering the non HDL cholesterol value. So the aim was to study if non HDL cholesterol has got significant role in assessing CVA risk in a population with relatively low LDL levels. It is generally recommended in high doses 80 mg/day in the first month of acute coronary syndrome.

Then gradual tapering is advised and dose is tapered to meet LDL goals. In CAD patients the LDL goal is set at 70 mg/dl. It can be prescribed at any time of the day preferably at night because the enzyme HMG Co A reductase is secreted maximally at night. Other cardiac drugs like beta blockers and thiazide diuretics affect lipid profile.

To have better standards for comparison all patients on atorvastatin therapy who took 10 mg/day were included in the study. The minimum intake was set at 1 year. But in our study it was concluded that the

majority of patients both cases and controls hadnot attained the goal LDL level. Only 2 out of 50 cases and 50 controls had attained the LDL target level which is less than 70 mg/dl. However the LDL levels were lesser than the levels in general population.

Why non HDL Cholesterol?

LDL cholesterol is widely recognised as the marker of coronary artery disease. Statins have good effect in lowering LDL cholesterol values. But still patients develop ischemic events. So the importance of looking beyond LDL cholesterol arises. **Further non HDL Cholesterol is a calculated value using total cholesterol and HDL both of which are got from direct measurements whereas LDL cholesterol is a predicted value using FRIEDWALDS equation in most of the labs in India like our lab. Non HDL cholesterol includes all the atherogenic particles in the lipid profile. Hence its considered to have a superior predictive value.**

The LDL value reported does not give the actual atherogenic LDL values. In our study hence we have focussed on non HDL cholesterol which is increasingly recognised as a significant correlate in various studies.

Why CAD was coupled with CVA?

The pathogenesis behind coronary artery disease and ischemic stroke is the same atherosclerosis. Since it's easy to recognise a second ischemic event at a different site than the same coronary arteries, this dual system analysis was conducted.

Why the duration of occurrence of ischemic events was chosen as 1 to 5 years?

I would like to state that this specific duration was chosen to stress the high chance of recurrent ischemic events in the study group and for chosing a control group who did not develop a cerebral ischemic event within the period.

AGE DISTRIBUTION:

In our study the mean age of the population was 66.4 years. The mean age of first incidence of a coronary event in our population is 53.2 years and that of CVA is 62.4 years. (meenaksi *et al*)[20]. In India we have early onset of ischemic events due to genetic factors.

SEX DISTRIBUTION

In our study males were more affected than females (29:21). This has been reported in various studies. Leading examples include studies by Elizabeth *et al*[10]. In the majority of studies the ratio is around 2:1. In our study the ratio is 29:21. The difference in results could be ignored due to

small sample size. This could be because of the greater prevalence of metabolic syndrome in females in Trichy district and also because of a slightly elderly population as a study group. Majority of women had attained menopause which removes cardio protective activity of oestrogen.

FAMILY HISTORY

In our study 38 (74%) CAD patients who developed CVA had positive family history for ischemic events and 28 (56%) of the controls who were CAD patients and did not develop CVA had positive family history. This was similar to the study conducted by hoseini *et al*[14]. The very high prevalence of family history is reported in Indian population so also the earlier onset of ischemic event by a decade due to genetic factors.

SMOKING

In our study 40% were smokers. Controls were matched for smoking. This indicates a high prevalence of ischemic events in people who smoke. This has been proved number of times in various studies examples include study done by Jeremy *et al.*[15]

ALCOHOLISM

In our study 40% were alcoholics. Controls were matched for alcohol intake. This indicates a high prevalence of ischemic events in

people who consume alcohol. This has been proved number of times in various studies examples include study done by michael *et al*.[21]

TOTAL CHOLESTEROL

In our study the average total cholesterol value among cases was 197.14. The average of the total cholesterol value among controls was found to be 180.34. The p value was found to be p = 0.0050 which was found to be statistically significant. The low values were due to the use of statins. This is in concordance with the study conducted on total cholesterol[30] by various studies and Cleveland heart society and ATP 3 guidelines.[31]

LDL CHOLESTEROL

In our study the average LDL cholesterol value among cases was 121.34 mg/dl. The average of the LDL cholesterol value among controls was found to be 98.72 mg/dl. Though this was low when compared to patients who developed CAD but who were not on STATIN therapy(which is 135-140mg/dl) [2,5,20,22] , only 4% of the total 50 % cases and 50% controls had attained the target LDL which is set at 70mg/dl. The p value was found to be p< 0.0001 which was found to be statistically significant. The relatively low values were due to the use of statins.

TRIGLYCERIDES

In our study the average triglyceride value among cases was 193.16. The average of the triglycerides value among controls was found to be 189.6. The p value was found to be 0.544 which was not found to be statistically significant. The low values were due to the use of statins. In the analysis by miler *et al* the average triglyceride value was 200.3 on patients on statin therapy.[22]

HDL CHOLESTEROL

In our study the average HDL cholesterol value among cases was 37.1 mg/dl. The average of the HDL cholesterol value among controls was found to be 43.7. The p value was found to be $p< 0.0001$ which was found to be statistically significant. This is in concordance with the study conducted on HDL cholesterol by chapman *et al* where the average HDL cholesterol was 36.84 for patients on statin therapy.[7]

NON HDL CHOLESTEROL

In our study the average non HDL cholesterol value among cases was 16O.04mg/dl. The average of the Non HDL cholesterol value among controls was found to be 136.64 mg/dl. The p value was found to be $p< 0.0001$ which was found to be statistically significant. Though the control group had low values of non HDL cholesterol it was not within the target range set by ATP 3 guidelines which is set at 100 mg/dl. This is

in concordance with the study conducted by Susan *et al* where the average non HDL cholesterol for patients on statin therapy was 137.2. This matches our control population.[30]

Pravin *et al*[39] conducted a study to stress the importance of non HDL Cholesterol on ischemic stroke patients. The results of the study were that the mean non HDL Cholesterol was 198.8 mg/dl. The mean non HDL cholesterol of controls was 129.42mg/dl. In this study and other similar studies the control population was not CAD patients on statin therapy. Hence exact comparison could not be made out. This indicates that the difference in non HDL cholesterol contributed significantly in the occurrence of a second ischemic event in the form of cerebrovascular accident in the study population.

SUMMARY

SUMMARY

Our study population had significantly low HDL, high Non HDL, high LDL values, high total cholesterol values and high BMI compared to controls. The Triglyceride matched the control population. The importance of non HDL cholesterol is stressed on patients with high triglycerides in various literatures. In our population though the triglycerides were not significantly elevated the non HDL cholesterol values were still significantly high. So it stresses the importance of routinely looking beyond LDL cholesterol in all patients. Non HDL cholesterol was not superior to LDL cholesterol but was equally significant.

Statins as a class reduce LDL cholesterol. They also reduce total cholesterol & triglycerides to a certain extent. But their effect on HDL cholesterol is not uniform. Atorvastatin has got no role in reducing non HDL cholesterol values. Only newer drugs with high potency including rosuvastatin and simvastatin elevate HDL Cholesterol and reduce non HDL cholesterol. The importance of non HDL cholesterol is well established in patients with elevated triglycerides and diabetes population. Our study stresses the importance of routinely focussing on non HDL Cholesterol as a parameter as it is more accurate as it’s got by deducting total cholesterol from HDL cholesterol both of which are

directly measured. Majority of labs report calculated LDL value using Friedwalds equation and it does not give us the clinically important atherogenic LDL particle level. LDL level is a predicted value.

In our study patients on atorvastatin therapy were chosen as we wanted to stress the importance of non HDL Cholesterol values on patients with LDL cholesterol values that were likely to be lower than the general population as they were on atorvastatin therapy. However since it was a case control study the dose of atorvastatin was not titrated to meet the target LDL values and the desired results could not be obtained. But still our study clearly establishes the definitive role of non HDL cholesterol on par with LDL cholesterol in assessing the risk of ischemic stroke. Drugs that reduce non HDL cholesterol include rosuvastatin, simvastatin, niacin and fibrates. However life style modifications are the most effective treatment strategy.

CONCLUSION

CONCLUSION

- Though LDL cholesterol is the most important factor in monitoring cerebro vascular risk status and subsequent follow up of risk reduction , the case is not always so.
- **In our study LDL cholesterol, HDL cholesterol and non HDL cholesterol had equal p values in predicting risk of ischemic strokes.**
- In spite of risk reduction with reduction of LDL cholesterol levels in certain sub group of patients the risk of atherosclerotic events remains high. Other factors like triglycerides, non HDL cholesterol, Apo lipoproteins, lipoprotein a and are important.
- Non HDL cholesterol has a significant contribution in risk assessment and goal monitoring in ischemic stroke patients.
- National cholesterol education program NCEP adult treatment panel ATP 3 recommends LDL as the primary target and non HDL as the secondary target. Since LDL reported by most of the labs is a calculated and predicted value they should be routinely encouraged to report the non HDL cholesterol value which is more accurate and physicians should routinely target non HDL cholesterol for treatment.

LIMITATIONS

LIMITAITONS

- Dose of atorvastatin was not titrated to the maximum to get LDL within target levels as it was a case control study.
- Low density cholesterol is a calculated value. Exact measurement of low density cholesterol particle was not done.
- Apolipoprotein B was not include in the study
- The presence of a second ischemic event in the coronary system was not included in the study
- Though the LDL Cholesterol values were low in the study population they had not reached the target set by the ATP 3 guidelines
- Though non HDL cholesterol among controls were low they were not in the target set by ATP 3 guidelines.
- The state of diabetes control was not assertained. But in view that diabetes itself contributes to increase risk of stherosclerosis by cholesterol pathway the fact may be ignored.
- Thes state of hypertensive was not assertained as it was a case control study.
- Our study is a study conducted with small sample size. The same results may not be obtained in the general population.

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BIBLIOGRAPHY

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PROFORMA

PROFORMA

Name : Age/Sex : Occupation :

Address : I.P NO :

Contact No : D.O.A :

D.O.D :

Chief complaints :

Presenting illness :

Past History :

Diagnosed as Coronary artery disease duration in years:

Diagnosed as diabetes duration in years:

Treatment History :

Statin therapy duration :

Personal History :

Family History :

General Examination :

Height :

Weight :

Waist circumference : :

Body mass Index :

Pallor :

Icterus :

Clubbing :

Cyanosis :

Lymphadenopathy :

Pedal Edema :

Vitals :

Temp :

Pulse :

BP :

Respiratory Rate :

JVP :

Systemic examination :

Respiratoy :

Cardiovascular :

Abdomen :

Central nervous system :

Investigations :

1. Complete blood count
2. blood sugar
3. Renal parameters –Blood urea, and Serum Creatinine
4. serum Electrolytes.
5. Fasting Lipid profile
6. ECG
7. CXR
8. CT Brain / MRI Brain
9. ECHO
10. Carotid Doppler Study

ABBREVIATIONS

ABREVIATIONS

ACAT	-	acyl co A cholesterol acetyl transferase
ATPIII	-	Adult Treatment Panel
BMI	-	Body Mass Index
BP	-	Blood Pressure
CAD	-	Coronary Artery Disease
CRP	-	C Reactive Protein
CT	-	Computerised tomography
CVA	-	Cerebrovascular accident
df	-	discriminative frequency
DM	-	Diabetes Mellitus
ECG	-	Electrocardiogram
ECHO	-	Echocardiography
ESR	-	Erythrocyte Sedimentation Rate
HDL	-	High density Lipoprotein
HT	-	Hypertension
LDL	-	Low Density Lipoprotein
MRFIT	-	Multiple Risk Factor Intervention Trial
MRI	-	magnetic resonance imaging
NPC1L	-	Niemen pick like protein
NSTEMI	-	Non ST Elevation Myocardial Infarction
P value	-	Probability value
PR	-	Pulse Rate
SD	-	Standard deviation
SREBP	-	Selective response element binding protein
SEM	-	Standard error of mean

STEMI	-	ST Elevation Myocardial Infarction
TC	-	Total Count
TLC	-	Therapeutic life style changes
VLDL	-	Very Low density lipoprotein
WBC	-	White blood cell
WHO	-	World Health Organization

MASTER CHART ABBREVIATIONS

F	-	Female
M	-	Male
HT	-	hypertension
DM	-	diabetes
S	-	Smoker
HDL	-	high density lipoprotein
A	-	alcoholic
Y	-	yes
TC	-	total cholesterol
N	-	no
MCA	-	middle cerebral artery infarct
PCS	-	posterior circulation stroke
LDL	-	low density lipoprotein
TGL	-	triglycerides
BMI	-	body mass index
ACA	-	anterior cerebral artery infarct
VLDL	-	very low density lipoprotein

MASTER CHART

cases	AGE	SEX	DM	HT	S/A	CVA TYPE	TC	HDL	NON	LDL	TGL	BMI	
1	52	m	y	y	s/a	mca	170	18	152	120	160	23.3	
2	45	M	y	y	s/a	mca	167	42	125	91	170	18.6	
3	60	f	y	y		mca	178	38	140	104	180	19.4	
4	65	m	y	y	s/a	aca	185	30	155	116	194	23.1	
5	64	f	n	y		mca	160	39	121	80	203	19.7	
6	58	m	y	y	s/a	mca	189	30	159	131	140	23.9	
7	68	m	y	y	s/a	mca	172	42	130	85	223	23.4	
8	75	m	n	y	s/a	mca	176	31	145	119	130	22.2	
9	64	f	n	n		mca	187	39	148	119	146	26	
10	67	m	n	n	s/a	mca	211	38	173	135	190	23.5	
11	65	m	n	n	s/a	mca	190	52	138	96	210	21.4	
12	57	m	n	n	s/a	mca	156	32	124	95	143	26.4	
13	54	m	n	n		mca	180	32	148	120	142	26.7	
14	58	f	n	n		pcs	156	32	124	86	190	21.8	
15	69	f	n	n		mca	189	45	144	108	180	26.8	
16	73	f	n	n		mca	221	42	179	152	134	26.9	
17	72	m	y	y		mca	214	43	171	124	234	27	
18	65	m	y	n	s/a	pcs	160	31	129	84	223	27.1	
19	68	m	n	n		mca	215	32	183	140	213	27.2	
20	58	m	n	n		mca	153	31	122	84	190	28	
21	65	m	y	y	s/a	mca	212	29	183	143	199	23.8	
22	64	m	n	y		mca	212	28	184	146	189	28.2	
23	67	m	n	n		ica	152	35	117	78	195	28.4	
24	74	m	n	n	s/a	mca	170	28	142	102	198	24.2	
25	54	m	y	y	s/a	mca	213	35	178	139	194	28.5	
26	68	m	n	n	s/a	pcs	152	34	118	82	180	28.6	
27	76	m	n	n	s/a	mca	152	25	127	85	210	28.9	
28	65	m	y	n	s/a	mca	190	32	158	115	213	29	
29	67	m	n	n		mca	231	32	199	153	231	29.4	
30	68	m	n	y	s/a	mca	212	34	178	134	221	29.8	
31	69	f	n	n	a	mca	198	35	163	119	221	29.8	
32	75	f	y	y		mca	198	35	163	125	190	28	
33	76	f	n	n		mca	197	36	161	123	192	29	
34	78	f	n	y	a	mca	189	38	151	112	195	27.4	
35	67	f	n	y		mca	198	39	159	119	198	30.3	
36	75	f	y	n		pcs	234	40	194	157	185	34	
37	68	f	n	n		mca	221	40	181	144	184	32.3	
38	75	m	n	n	s	mca	190	21	169	132	185	33.4	
39	69	f	n	n		mca	213	37	176	138	192	29	
40	74	f	y	y		mca	235	37	198	156	210	29.4	
41	74	f	n	n	a	mca	221	46	175	129	230	28.4	
42	76	f	n	n		mca	223	54	169	121	240	28.9	
43	65	f	y	n		mca	224	53	171	125	231	29	
44	63	m	n	y	s	mca	267	45	222	178	221	29	
45	65	m	n	n	s	mca	230	34	196	150	231	29.4	
46	68	m	n	n		mca	243	36	207	162	224	29.5	
47	74	f	n	n		mca	231	50	181	137	221	29.3	
48	56	f	y	n		mca	230	52	178	134	221	29.4	
49	53	f	n	n		mca	220	54	166	139	134	29.5	
50	75	m	n	n		mca	170	42	128	100	212	25.5	

contro	AGE	SEX	DM	HT	S/A	TC	HDL	NON HDL	LDL	TGL	BMI	
1	52	m	y	y	s/a	201	17	184	152	160	21.6	
2	45	m	y	y	s/a	213	50	163	128	174	24.4	
3	60	f	y	y		203	46	157	120	183	21.4	
4	65	m	y	y	s/a	202	47	155	117	191	24	
5	64	f	n	y		213	45	168	129	195	24.3	
6	58	m	y	y	s/a	198	46	152	124	142	20.6	
7	68	m	y	y	s/a	170	36	134	89	223	28	
8	75	m	n	y	s/a	220	37	183	157	132	23.1	
9	64	f	n	n		178	44	134	100	168	20.4	
10	67	m	n	n	s/a	178	53	125	87	188	23.3	
11	65	m	n	n	s/a	190	54	136	107	143	24.5	
12	57	m	n	n	s/a	196	52	144	115	143	24.5	
13	54	m	n	n		152	45	107	79	141	19.8	
14	58	f	n	n		189	40	149	110	196	28.9	
15	69	f	n	n		178	50	128	91	184	24.6	
16	73	f	n	n		156	46	110	83	134	28.6	
17	72	m	y	y		200	47	153	125	138	21.8	
18	65	m	y	n	s/a	163	38	125	82	214	24.7	
19	68	m	n	n		178	36	142	99	213	28.9	
20	58	m	n	n		176	31	145	107	190	21.4	
21	65	m	y	y	s/a	221	42	179	139	199	23.8	
22	64	m	n	y		176	38	138	101	187	23.9	
23	67	m	n	n		175	35	140	101	195	20.4	
24	74	m	n	n	s/a	190	45	145	106	197	27	
25	54	m	y	y	s/a	152	43	109	72	187	24.3	
26	68	m	n	n	s/a	176	41	135	99	180	21.4	
27	76	m	n	n	s/a	201	44	157	114	214	23.8	
28	65	m	y	n	s/a	153	64	89	46	213	22.1	
29	67	m	n	n		154	32	122	79	213	27.8	
30	68	m	n	y	s/a	180	38	142	99	214	27.9	
31	69	f	n	n	a	160	35	125	83	212	24.4	
32	75	f	y	y		153	38	115	77	190	24.5	
33	76	f	n	n		205	54	151	113	192	28.9	
34	78	f	n	y	a	187	44	143	104	195	24.3	
35	67	f	n	y		152	53	99	59	198	24.5	
36	75	f	y	n		190	46	144	107	185	28	
37	68	f	n	n		200	45	155	118	184	26.7	
38	75	m	n	n	s	152	28	124	87	185	26.9	
39	69	f	n	n		153	45	108	70	192	28	
40	74	f	y	y		156	45	111	69	210	27.8	
41	74	f	n	n	a	178	46	132	88	221	27	
42	76	f	n	n		160	45	115	73	212	26	
43	65	f	y	n		213	57	156	110	231	27	
44	63	m	n	y	s	176	57	119	75	221	28	
45	65	m	n	n	s	160	34	126	80	231	30.1	
46	68	m	n	n		170	35	135	90	224	28.7	
47	74	f	n	n		180	53	127	83	221	32	
48	56	f	y	n		186	54	132	88	221	29	
49	53	f	n	n		184	54	130	103	134	29.6	
50	75	m	n	n		170	35	135	101	170	27.4	

CONSENT FORM

CONSENT FORM

Name of Researcher:

Please initial box

1. I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐

3. I understand that any information given by me may be used in future reports, articles or presentations by the research team. ☐

4. I understand that my name will not appear in any reports, articles or presentations. ☐

5. I agree to take part in the above study. ☐

_____	_____	
	_____	
Name of Participant	Date	Signature
_____	_____	
	_____	
Researcher	Date	Signature